Global Asymptotic Properties of a Heroin Epidemic Model with Treat-Age *

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Abstract

In this paper, a model for the use of heroin with treat-age is formulated based on the principles of mathematical epidemiology. The model accounts for relapse rate that depends on how long the host has been in treatment for heroin addiction. An explicit formula for the reproductive number of the heroin spread is obtained. By using the method of Lyapunov functional, we established the dynamical properties of the heroin epidemic model, and the results show that the global dynamics of the model is completely determined by the basic reproduction number. It is shown that the drug-free equilibrium is locally and globally asymptotically stable if the basic reproduction number is less than one. In addition, the heroin spread system is uniform persistence and the unique drug spread equilibrium is locally and globally asymptotically stable if the basic reproduction number is greater than one.

Key words: Heroin epidemic model; treat-age; drug-free equilibrium; drug spread equilibrium; basic reproduction number; Lyapunov functional.

MSC: 37C75; 45D05

1 Introduction

Heroin is an opiate drug that is synthesized from morphine, a naturally occurring substance extracted from the seed pod of the Asian opium poppy plant. Heroin usually appears as a white or brown powder or as a black sticky substance, known as "black tar heroin"[1]. Over the past two decades, China has faced a dramatic increase in illicit drug abuse accompanying

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rapid economic reform and development[2]. In 2000, heroin still was the first choice among drug users (rising from 83.4 percent in 1993 to 95.9 percent in 2000), and its most frequent routes of delivery were intravenous injection (25 percent) and inhalation[3]. Heroin users are at high risk for addiction that it is estimated that about 23 percent of individuals who use heroin become dependent on it. The spread of heroin habituation and addiction presents many of the well-known phenomena of epidemics, including rapid diffusion and clear geographic boundaries[4, 5, 6]. In addition to their deleterious somatic and psychological effects, heroin abuse and dependence constitute one of the most important modes of transmitting Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) [7, 8, 9]. Statistical information for drug abuse, including heroin abuse, is given by various governmental agencies, including National Institute on Drug Abuse in the US. But it is unrealistic to repeat the experiment on the human body for obtaining the statistic data. However, mathematical modelling plays important role in understanding and combating drug addiction problems. Models are very useful tools to predict how classes of drug users behave, and provide suggestions for treatment strategies.

In recent years, many mathematical models have been developed to describe the heroin epidemic ([10-13]). In these models, the population is devided into three classes, namely susceptibles, heroin drug users not in treatment, and heroin drug users undergoing treatment. These classes are denoted by $S(t), U_1(t)$ and $U_2(t)$, respectively. All prior heroin epidemic models are ODE models and address treatment strategies. The authors in [10, 11] considered a susceptible, untreated used, treated users model with standard incidence rate and showed that the steady states of the model of heroin epidemics are stable. Wang et al in[12] considered the mass action incidence rate and proved that the drug-free equilibrium and the unique endemic equilibrium is globally asymptotically stable under some conditions. Samanta [13] considered a nonautonomous heroin epidemic model with time delay. However, all these studies did not consider the influence of the treat-age for the heroin users during the treatment. In fact, studies, such as Elvebac et al. in [14], suggest that disease transmission models with age-dependent rates are more realistic than those that do not consider age-dependent rates. To address the need to involve treat-age in heroin studies, in this paper, we present a heroin epidemic model with treat-age, based on the principles of mathematical epidemiology. The model incorporates relapse rate that depend on how long the host has been in treatment. We analyze the existence and stability of the equilibria of the model and characterize the threshold conditions of the heroin epidemic model with an explicit formula for the reproductive number. It is shown that the existence, local and global asymptotical stability of equilibria is completely determined by the basic reproduction number. By using a class of global Lya-

punov functionals we obtain the dynamics of the heroin epidemic model. It is shown that the drug-free equilibrium is globally asymptotically stable if the basic reproduction number is less than one. In addition, the heroin spread system is uniform persistent and the unique drug spread equilibrium is globally asymptotically stable if the basic reproduction number is greater than one.

The paper is organized as follows. In the next section we mainly formulate the heroin epidemic model with treat-age, present the basic reproduction number, investigate the existence of the equilibrium, and then state the main results of the paper. In order to prove the results on the global stability of the drug spread equilibrium, in section 3 we present some preliminary results about the uniform persistence of the heroin spread system and about the existence of global attractors. In addition, the local asymptotic stability of the drug-free equilibrium and the drug spread equilibrium is also discussed in this section. In section 4 the proof of the results on the global asymptotic stability of the drug-free equilibrium and drug spread equilibrium is investigated by the use of a appropriate Lyapunov functional. Finally, we summarize our results in Section 5.

2 Model formulation and main results

On the premise that drug use follows a process that can be modelled in a similar way to the modelling of disease[15, 16], a mathematical epidemiological treatment model of drug use may yield insights on the progression through the drug users career, from initiation to habitual use, treatment, relapse and eventual recovery. It is of course critical to understand, insofar as it is possible, the process being modelled. Information from the ROSIE study [17] and feedback from professionals in addiction-related areas were fundamental in developing the model. In order to investigate the influence of the treat-age on the spread of the heroin epidemic, we divide the population into three mutually-exclusive compartments (subgroups), namely, the susceptibles, the drug users not in treatment and the drug users in treatment, denoted by $S(t), U_1(t)$ and $U_2(\theta, t)$, respectively. Here the parameter θ denotes the treat-age of the heroin drug users undergoing treatment at time t. On the one hand, we assume that drug users not in treatment are only infectious to susceptibles and drug users in treatment are not infectious to susceptibles. Moreover, drug users would return to untreated drug user class after cessation of a drug treatment programme. On the other hand, we assume that every individual in the population has an equal chance of encountering any other individual and all members of the population are equally susceptible to drug addiction. Motivated by

[10], we formulate the heroin epidemic model with treat-age as follows:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \beta S(t)U_1(t) - \mu S(t), \\ \dfrac{dU_1(t)}{dt} = \beta S(t)U_1(t) - \big(\mu + \delta_1 + p\big)U_1(t) + \displaystyle\int_0^\infty k(\theta)U_2(\theta,t)d\theta, \\ \dfrac{\partial U_2(\theta,t)}{\partial \theta} + \dfrac{\partial U_2(\theta,t)}{\partial t} = -\big(\mu + \delta_2 + k(\theta)\big)U_2(\theta,t), \end{cases} \tag{2.1}$$

with the following boundary and initial conditions:

$$\begin{cases} U_2(0,t) = p\ U_1(t), \\ \quad S(0) = S^0, \quad U_1(0) = U_1^0, \quad U_2(\theta,0) = U_2^0(\theta), \end{cases} \tag{2.2}$$

where $S^0, U_1^0 \in \mathbb{R}_+$, and $U_2^0(\theta) \in L^1_+\big((0,+\infty),\ \mathbb{R}\big)$.

The meanings of all parameters in the above model are as follows:

• $S(t)$: the number of susceptible individuals in the population at time t;

• $U_1(t)$: the number of drug users not in treatment; initial and relapsed drug users;

• $U_2(\theta,t)$: the number of drug users in treatment with age θ at time t;

• Λ: the number of individuals in the general population entering the susceptible population;

• β: the rate of becoming a drug user;

• p: 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;

• $k(\theta)$: the probability of a drug user in treatment with treat-age θ relapsing to untreated use;

• μ: the natural death rate of the general population.

All parameters are nonnegative, $\Lambda > 0$, and $\mu > 0$. We further assume that the parameter-functions $k(\theta)$ belongs to $L^\infty_+\big((0,\infty),\mathbb{R}\big) \setminus \{0_{L^\infty}\}$.

Define the space of functions

$$X = \mathbb{R} \times \mathbb{R} \times L^1(0,\infty), \qquad X_+ = \mathbb{R}_+ \times \mathbb{R}_+ \times L^1_+(0,\infty),$$

where $L^1_+(0,\infty)$ is the space of functions on $(0,\infty)$ that are nonnegative and Lebesgue integrable, equipped with the norm

$$\big|\big|(S,U_1,U_2(\theta))\big|\big|_{X_+} = \big|S\big| + \big|U_1\big| + \int_0^\infty \big|U_2(\theta)\big|d\theta.$$

The norm has the biological interpretation of giving the total population size.

The initial conditions in (2.2) that belong to the positive cone X_+ can be rewritten as

$$\big(S^0, U_1^0, U_2^0(\cdot)\big) \in X_+.$$

Using standard methods, we can verify the existence and uniqueness of solutions to model (2.1) with the boundary and initial conditions (2.2) (see Webb [18] and Iannelli [19]). Moreover, we can show that all solutions of system (2.1) with nonnegative initial conditions (2.2) that belong to the positive cone X_+ will remain nonnegative and bounded for all $t > 0$.

Letting

$$U_2(t) = \int_0^\infty U_2(\theta,t)d\theta, \quad \text{and} \quad N(t) = S(t) + U_1(t) + U_2(t).$$

Adding all equations of system (2.1) we have

$$\begin{aligned}
&\frac{d}{dt}\left(S(t) + U_1(t) + \int_0^\infty U_2(\theta,t)d\theta\right)\\
&= \frac{dS(t)}{dt} + \frac{dU_1(t)}{dt} + \int_0^\infty \frac{\partial U_2(\theta,t)}{\partial t}d\theta\\
&= \Big(\Lambda - \beta S(t)U_1(t) - \mu S(t)\Big) + \left(\beta S(t)U_1(t) - \big(\mu+\delta_1+p\big)U_1(t) + \int_0^\infty k(\theta)U_2(\theta,t)d\theta\right)\\
&\quad + \int_0^\infty \left\{-\frac{\partial U_2(\theta,t)}{\partial\theta} - \big(\mu+\delta_2+k(\theta)\big)U_2(\theta,t)\right\}d\theta\\
&= \Lambda - \mu\left(S(t) + U_1(t) + \int_0^\infty U_2(\theta,t)d\theta\right) - pU_1(t) - U_2(\theta,t)\Big|_{\theta=0}^{\theta=\infty} - \delta_1 U_1(t)\\
&\quad -\delta_2\int_0^\infty U_2(\theta,t)d\theta\\
&\le \Lambda - \mu\left(S(t) + U_1(t) + \int_0^\infty U_2(\theta,t)d\theta\right).
\end{aligned}$$

So we have

$$\frac{dN(t)}{dt} \le \Lambda - \mu N(t), \tag{2.3}$$

and therefore

$$\limsup_{t\to+\infty} N(t) \le \frac{\Lambda}{\mu}.$$

Furthermore, if $N(t) \le \dfrac{\Lambda}{\mu}$ is satisfied for some $t = t_0 \in \mathbb{R}$, then it is satisfied for all $t \ge t_0$. Therefore, the system (2.1) is point dissipative.

Denote

$$\mathcal{S} = \left\{ (S, U_1, U_2) \in X_+ \;\middle|\; S(t) + U_1(t) + \int_0^\infty U_2(\theta, t)d\theta \leq \frac{\Lambda}{\mu} \right\}.$$

We know $\mathcal{S}$ attracts all points in X. Then the set $\mathcal{S}$ is maximum positively invariant set for system (2.1).

Finally, since the exit rate from the drug users in treatment compartment is given by $\mu+\delta_2+k(\theta)$, then the probability of still being the drug users in treatment after θ time units is given by

$$\Pi(\theta) = e^{-\int_0^\theta \left(\mu+\delta_2+k(\sigma)\right)d\sigma}.$$

Therefore, $K = \int_0^\infty k(\theta)\Pi(\theta)d\theta$ is the probability of relapsing the drug users in treatment class.

In order to find any positive equilibria, we first determine the basic reproduction number $\mathcal{R}_0$ of the heroin epidemic model [20], which is given by the following expression:

$$\mathcal{R}_0 = \frac{\beta \cdot \frac{\Lambda}{\mu}}{(\mu + \delta_1 + p) - pK}. \tag{2.4}$$

To interpret formula (2.4) as a secondary number of heroin users produced by one heroin user, that is $\mathcal{R}_0$, we note that the average time in the drug users not in treatment class on the first pass is $\frac{1}{\mu+\delta_1+p}$ and the probability of surviving this class is $\frac{p}{\mu+\delta_1+p}$. Since K is the probability of relapsing the drug users in treatment class, the total average time in the drug users not in treatment class (on multiple passes) is

$$\frac{1}{\mu+\delta_1+p}\left[1 + \frac{p}{\mu+\delta_1+p}\cdot K + \left(\frac{p}{\mu+\delta_1+p}\cdot K\right)^2 + \cdots\right] = \frac{1}{(\mu+\delta_1+p) - pK}. \tag{2.5}$$

Multiplying this by $\beta\cdot\frac{\Lambda}{\mu}$ gives $\mathcal{R}_0$, which is the average number of new drug users produced by a typical drug user not in treatment introduced into an entirely susceptible population[21, 22]. Thus, $\mathcal{R}_0$ is the basic reproduction number which acts as a threshold as is shown in the following result.

Now let us investigate the existence of the steady states of system (2.1). For any steady state $\left(S^*, U_1^*, U_2^*(\theta)\right)$ of system (2.1), it should satisfy the following equalities:

$$\begin{cases} 0 = \Lambda - \beta S^* U_1^* - \mu S^*, \\ 0 = \beta S^* U_1^* - \left(\mu + \delta_1 + p\right)U_1^* + \displaystyle\int_0^\infty k(\theta)U_2^*(\theta)d\theta, \\ \dfrac{dU_2^*(\theta)}{d\theta} = -\left(\mu + \delta_2 + k(\theta)\right)U_2^*(\theta), \\ U_2^*(0) = pU_1^*. \end{cases} \tag{2.6}$$

Solving the third equation of (2.6), we get

$$U_2^*(\theta) = U_2^*(0)e^{-\int_0^\theta(\mu+\delta_2+k(\sigma))d\sigma} = pU_1^*\ \Pi(\theta). \tag{2.7}$$

If $U_1^* = 0$, then we have $U_2^*(\theta) = 0$ from (2.7). From the first equation of (2.6), we obtain

$$S_0^* = \frac{\Lambda}{\mu}.$$

Obviously, system (2.1) always has the drug-free equilibrium, in which there are no drug users present, given by

$$E_0 = \big(S_0^*, 0, 0\big), \quad S_0^* = \frac{\Lambda}{\mu}. \tag{2.8}$$

If $U_1^* \neq 0$, substituting (2.7) into the second equation of (2.6), we have

$$\beta S^* = \big(\mu + \delta_1 + p\big) - pK, \tag{2.9}$$

or

$$S^* = \frac{\big(\mu + \delta_1 + p\big) - pK}{\beta} = \frac{1}{\mathcal{R}_0} \cdot \frac{\Lambda}{\mu}. \tag{2.10}$$

Substituting the result into the first equation of (2.6), yields

$$U_1^* = \frac{\Lambda - \mu S^*}{\beta S^*} = \frac{\mu}{\beta} \cdot (\mathcal{R}_0 - 1). \tag{2.11}$$

It can be easily seen from the expressions of S^*, U_1^* and $U_2^*(\theta)$ that system (2.1) has a unique drug spread equilibrium $E^*\big(S^*, U_1^*, U_2^*(\theta)\big)$ if and only if $\mathcal{R}_0 > 1$. Summarizing the discussions above, we have the following theorem.

Theorem 2.1 *The system (2.1) can have up to two equilibria. More precisely, we have*
(1) The drug-free equilibrium $E_0\big(\frac{\Lambda}{\mu}, 0, 0\big)$ *always exists.*
(2) If $\mathcal{R}_0 > 1$*, there exists a unique drug spread equilibrium* $E^*\big(S^*, U_1^*, U_2^*(\theta)\big)$*, where*

$$S^* = \frac{1}{\mathcal{R}_0} \cdot \frac{\Lambda}{\mu}, \quad U_1^* = \frac{\mu}{\beta} \cdot \big(\mathcal{R}_0 - 1\big), \quad U_2^*(\theta) = pU_1^*\ \Pi(\theta).$$

In order to state the main results of the paper, we set

$$\bar{\theta} = \inf\left\{\ \theta : \int_\theta^\infty k(\theta)d\theta = 0\right\}.$$

Since the functions $k(\theta)$ belong to $L_+^\infty\big((0,+\infty),\ \mathbb{R}\big) \setminus \big\{0_{L^\infty}\big\}$, we have $\bar{\theta} > 0$. Furthermore, we let

$$\hat{\mathcal{M}_0} := \left\{ \begin{pmatrix} U_1(t) \\ U_2(\cdot, t) \end{pmatrix} \in \mathbb{R}_+ \times L_+\big((0,+\infty),\ \mathbb{R}\big) :\ U_1(t) > 0 \ \text{ or } \ \int_0^{\bar{\theta}} U_2(\theta, t)d\theta > 0 \right\},$$

and define

$$\mathcal{M}_0 := \mathbb{R}_+ \times \hat{\mathcal{M}}_0, \quad \partial\mathcal{M}_0 := \mathbb{R}_+ \times \mathbb{R}_+ \times L_+\big((0,+\infty),\ \mathbb{R}\big) \setminus \mathcal{M}_0.$$

Now we are able to state the main results of the paper.

Theorem 2.2 *If $\mathcal{R}_0 < 1$, then the drug-free equilibrium $E_0(\frac{\Lambda}{\mu}, 0, 0)$ is the unique equilibrium of system (2.1), and it is globally stable.*

Theorem 2.3 *Assume that $\mathcal{R}_0 > 1$, then the drug-free equilibrium $E_0(\frac{\Lambda}{\mu}, 0, 0)$ is globally asymptotically stable in $\partial\mathcal{M}_0$, and the unique drug spread equilibrium $E^*\big(S^*, U_1^*, U_2^*(\theta)\big)$ of system (2.1) is globally asymptotically stable in $\mathcal{M}_0$.*

3 Preliminary results and uniform persistence

In this section, we first reformulate system (2.1) as a Volterra equation by use of Volterra formulation (see Webb [18] and Iannelli [19]). Then we reformulate system (2.1) as a non-densely defined semilinear Cauchy problem in order to apply integrated semigroup theory (see Thieme [23]). Finally, by using the uniform persistence theory for abstract dynamical systems, we present some results about uniform persistence and the existence of global attractors.

3.1 Volterra formulation

The Volterra integral formulation of age-structured models has been used successfully in various contexts and provides explicit (or implicit) formulas for the solutions of age-structure models [24].

By using Volterra formulation, we integrate along the characteristic lines $t - \theta = \text{const.}$ for all $t > 0$, and solve the terms $U_2(\theta, t)$ as the following expressions:

$$U_2(\theta,t) = \begin{cases} U_2(t-\theta,0)\Pi(\theta) = pU_1(t-\theta)\Pi(\theta), & t > \theta, \\ U_2^0(\theta-t)\dfrac{\Pi(\theta)}{\Pi(\theta-t)}, & t < \theta. \end{cases} \tag{3.1}$$

Thus the system (2.1) with the boundary and initial conditions (2.2) can be rewritten as the following Volterra type equations:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \beta S(t)U_1(t) - \mu S(t), \\ \dfrac{dU_1(t)}{dt} = \beta S(t)U_1(t) - \big(\mu + \delta_1 + p\big)U_1(t) + \displaystyle\int_0^\infty k(\theta)U_2(\theta,t)d\theta, \\ U_2(\theta,t) = \begin{cases} pU_1(t-\theta)\Pi(\theta), & t > \theta, \\ U_2^0(\theta-t)\dfrac{\Pi(\theta)}{\Pi(\theta-t)}, & t < \theta. \end{cases} \end{cases} \tag{3.2}$$

3.2 Integrated semigroup formulation

We now use the approach introduced by Thieme [23] to reformulate the system (2.1) with the boundary and initial conditions (2.2) as a semilinear Cauchy problem. In order to take into account the boundary condition, we extend the state space by considering

$$\mathcal{X} = \mathbb{R} \times \mathbb{R} \times \mathcal{Y}, \qquad \text{where } \mathcal{Y} = \mathbb{R} \times L^1\big((0,+\infty),\mathbb{R}\big)$$

endowed with the usual product norm, and set

$$\mathcal{X}_0 = \mathbb{R} \times \mathbb{R} \times \mathcal{Y}_0, \qquad \mathcal{X}_+ = \mathbb{R}_+ \times \mathbb{R}_+ \times \mathcal{Y}_+,$$

where

$$\mathcal{Y}_0 = \big\{0\big\} \times L^1\big((0,+\infty),\mathbb{R}\big), \qquad \mathcal{Y}_+ = \mathbb{R}_+ \times L^1_+\big((0,+\infty),\mathbb{R}\big),$$

and

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

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

$$A\begin{pmatrix} S \\ U_1 \\ \begin{pmatrix} 0 \\ U_2 \end{pmatrix} \end{pmatrix} = \begin{pmatrix} -\mu S \\ -\big(\mu+\delta_1+p\big)U_1 \\ \begin{pmatrix} -U_2(0) \\ -U_2' - \big(\mu+\delta_2+k(\theta)\big)U_2 \end{pmatrix} \end{pmatrix}.$$

with

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

where $W^{1,1}$ is a Sobolev space, and we define the non-linear map $F : \mathcal{X}_0 \to \mathcal{X}$ by

$$F\begin{pmatrix} S \\ U_1 \\ \begin{pmatrix} 0 \\ U_2 \end{pmatrix} \end{pmatrix} = \begin{pmatrix} \Lambda - \beta S(t)U_1(t) \\ \beta S(t)U_1(t) + \displaystyle\int_0^\infty k(\theta)U_2(\theta,t)d\theta \\ \begin{pmatrix} pU_1(t) \\ 0_{L^1} \end{pmatrix} \end{pmatrix}.$$

Then by defining

$$v(t) = \begin{pmatrix} S(t) \\ U_1(t) \\ \begin{pmatrix} 0 \\ U_2(\cdot,t) \end{pmatrix} \end{pmatrix},$$

we can reformulated the PDE problem (2.1) with the boundary and initial conditions (2.2) as the following abstract Cauchy problem:

$$\frac{dv(t)}{dt} = Av(t) + F(v(t)) \tag{3.3}$$

for $t \geq 0$ and $v(0) = v_0 \in \mathcal{X}_{0+}$.

By using the results in Thieme [23] and Magal [25] (see Magal and Ruan [26] for more results), we derive the existence and the uniqueness of the semiflow $\{U(t)\}_{t\geq 0}$ on $\mathcal{X}_{0+}$ generated by system (3.3). By identifying $\big(S(t), U_1(t), 0, U_2(\cdot,t)\big)$ with $\big(S(t), U_1(t), U_2(\cdot,t)\big)$, it can be proved that this semiflow coincides with the one generated by using the Volterra integral formulation. Moreover, by using (2.3), we deduce that the set

$$\tilde{B} = \left\{ \begin{pmatrix} S \\ U_1 \\ \begin{pmatrix} 0 \\ U_2 \end{pmatrix} \end{pmatrix} \in \mathcal{X}_{0+} : S + U_1 + \int_0^\infty U_2(\theta)d\theta \leq \frac{\Lambda}{\mu} \right\}$$

is positively invariant absorbing set under this semiflow $\{U(t)\}_{t\geq 0}$ on $\mathcal{X}_{0+}$; that is to say that

$$U(t)\tilde{B} \subseteq \tilde{B},$$

and for each $x = \big(S^0, U_1^0, 0, U_2^0(\theta)\big) \in \mathcal{X}_{0+}$,

$$d\big(U(t)x, B\big) := \inf_{y\in\tilde{B}} \big\|U(t)x - y\big\| \to 0, \text{ as } t \to 0.$$

It follows that the semiflow $\{U(t)\}_{t\geq 0}$ is bounded dissipative on $\mathcal{X}_{0+}$(see Hale [27]). Furthermore, the semiflow $\{U(t)\}_{t\geq 0}$ is asymptotically smooth (see Webb [18], Magal and Thieme [28], Thieme and Vrabie [29]). As a consequence of the results on the existence of global attractors in Hale [27], we obtain the following theorem.

Theorem 3.1 *The system (3.3) generates a unique continuous semiflow $\{U(t)\}_{t\geq 0}$ on $\mathcal{X}_{0+}$ that is asymptotically smooth and bounded dissipative. Furthermore, the semiflow $\{U(t)\}_{t\geq 0}$ has a global attractor $\mathcal{A}$ in $\mathcal{X}_{0+}$ which attracts the bound sets of $\mathcal{X}_{0+}$.*

3.3 Local stability of the equilibria

In this subsection, we mainly prove the local stability of the equilibria whose existence have been stated in Theorem 2.1. One can refer to some relevant references [30, 31, 32, 33] for the analysis of local stability.

First, let us investigate the local stability of the drug-free equilibrium E_0 and we have the following Theorem 3.2.

Theorem 3.2 *The drug-free equilibrium E_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

Proof. Introducing the perturbation variables, i.e., letting

$$S(t) = \frac{\Lambda}{\mu} + x(t), \quad U_1(t) = y(t), \quad U_2(\theta,t) = z(\theta,t),$$

and linearizing the system (2.1) at the point E_0, we obtain the following system

$$\begin{cases} \dfrac{dx(t)}{dt} = -\beta\dfrac{\Lambda}{\mu}y(t) - \mu x(t), \\ \dfrac{dy(t)}{dt} = \beta\dfrac{\Lambda}{\mu}y(t) - \big(\mu + \delta_1 + p\big)y(t) + \displaystyle\int_0^\infty k(\theta)z(\theta,t)d\theta, \\ \dfrac{\partial z(\theta,t)}{\partial\theta} + \dfrac{\partial z(\theta,t)}{\partial t} = -\big(\mu + \delta_2 + k(\theta)\big)z(\theta,t), \\ z(0,t) = py(t). \end{cases} \tag{3.4}$$

To analyze the asymptotic behavior around E_0, we look for solutions of the form

$$x(t) = \bar{x}e^{\lambda t},\ y(t) = \bar{y}e^{\lambda t},\ z(\theta,t) = \bar{z}(\theta)e^{\lambda t},$$

where $\bar{x},\ \bar{y}$ and $\bar{z}(\theta)$ are to be determined. Thus, we can consider the following eigenvalue problem:

$$\begin{cases} (\lambda+\mu)\bar{x} = -\beta\dfrac{\Lambda}{\mu}\bar{y}, \\ \big(\lambda + \mu + \delta_1 + p\big)\bar{y} = \beta\dfrac{\Lambda}{\mu}\bar{y} + \displaystyle\int_0^\infty k(\theta)\bar{z}(\theta)d\theta, \\ \dfrac{d\bar{z}(\theta)}{d\theta} = -\big(\lambda + \mu + \delta_2 + k(\theta)\big)\bar{z}(\theta), \\ \bar{z}(0) = p\bar{y}. \end{cases} \tag{3.5}$$

Solving the third equation of (3.5), we get

$$\bar{z}(\theta) = \bar{z}(0)e^{-\lambda\theta}\cdot e^{-\int_0^\theta(\mu+\delta_2+k(\sigma))d\sigma} = p\bar{y}\cdot e^{-\lambda\theta}\cdot\Pi(\theta). \tag{3.6}$$

Substituting (3.6) into the second equation of (3.5) and cancelling $\bar{y}$ (for $\bar{y}\neq 0$), we get

$$p\int_0^\infty k(\theta)e^{-\lambda\theta}\Pi(\theta)d\theta = \lambda+\mu+\delta_1+p-\beta\frac{\Lambda}{\mu}. \tag{3.7}$$

We also have

$$1 = \frac{\beta\dfrac{\Lambda}{\mu}}{\lambda+\mu+\delta_1+p-p\displaystyle\int_0^\infty k(\theta)e^{-\lambda\theta}\Pi(\theta)d\theta}. \tag{3.8}$$

Define a function $\mathcal{H}(\lambda)$ to be the right-hand side above. Obviously, $\mathcal{H}(\lambda)$ is a continuously differentiable function with $\lim_{\lambda\to\infty}\mathcal{H}(\lambda) = 0$. By direct computing, it is easy to show that $\mathcal{H}'(\lambda) < 0$, that is, $\mathcal{H}(\lambda)$ is a decreasing function of λ. Hence, any real solution of Eq.(3.8) is negative if $\mathcal{H}(0) < 1$, and positive if $\mathcal{H}(0) > 1$. Hence, if $\mathcal{H}(0) > 1$, the drug-free equilibrium is unstable.

Next, we show that Eq.(3.8) has no complex solutions with nonnegative real part if $\mathcal{H}(0) < 1$. Suppose $\mathcal{H}(0) < 1$. Assume that $\lambda = a_1 + ib_1$ $(a_1, b_1 \in \mathbb{R}$, i is the imaginary unit) is a complex solution of equation (3.8) with $a_1 > 0$. Then

$$1 = |\mathcal{H}(\lambda)| \leq \mathcal{H}(a_1) \leq \mathcal{H}(0) < 1.$$

This is impossible. Thus, every solution of Eq.(3.8) must have a negative real part. Therefore, the drug-free equilibrium E_0 is locally asymptotically stable if $\mathcal{H}(0) < 1$.

Noticing that $\mathcal{H}(0) = \mathcal{R}_0$, we conclude that the drug-free equilibrium E_0 is asymptotically stable if $\mathcal{R}_0 < 1$ and is unstable if $\mathcal{R}_0 > 1$. This completes the proof of Theorem 3.2. $\square$

Now we investigate the local stability of the drug spread equilibrium E^*. We have the following result.

Theorem 3.3 *The drug spread equilibrium E^* is locally asymptotically stable if $\mathcal{R}_0 > 1$.*

Proof. Introducing the perturbation variables, i.e., letting:

$$S(t) = x(t) + S^*, \quad U_1(t) = y(t) + U_1^*, \quad U_2(\theta, t) = z(\theta, t) + U_2^*(\theta),$$

and linearizing the system (2.1) about E^*, we obtain the following system

$$\begin{cases} \dfrac{dx(t)}{dt} = -\beta S^* y(t) - \beta U_1^* x(t) - \mu x(t), \\ \dfrac{dy(t)}{dt} = \beta S^* y(t) + \beta U_1^* x(t) - \big(\mu + \delta_1 + p\big) y(t) + \displaystyle\int_0^\infty k(\theta) z(\theta, t) d\theta, \\ \dfrac{\partial z(\theta, t)}{\partial \theta} + \dfrac{\partial z(\theta, t)}{\partial t} = -\big(\mu + \delta_2 + k(\theta)\big) z(\theta, t), \\ z(0, t) = p y(t). \end{cases} \tag{3.9}$$

To analyze the asymptotic behavior around E^*, we look for solutions of the form

$$x(t) = \bar{x} e^{\lambda t}, \ y(t) = \bar{y} e^{\lambda t}, \ z(\theta, t) = \bar{z}(\theta) e^{\lambda t},$$

where $\bar{x}$, $\bar{y}$ and $\bar{z}(\theta)$ are to be determined. Thus, we can consider the following eigenvalue problem:

$$\begin{cases} (\lambda + \mu)\bar{x} = -\beta S^* \bar{y} - \beta U_1^* \bar{x}, \\ \big(\lambda + \mu + \delta_1 + p\big)\bar{y} = \beta S^* \bar{y} + \beta U_1^* \bar{x} + \displaystyle\int_0^\infty k(\theta) \bar{z}(\theta) d\theta, \\ \dfrac{d\bar{z}(\theta)}{d\theta} = -\big(\lambda + \mu + \delta_2 + k(\theta)\big) \bar{z}(\theta), \\ \bar{z}(0) = p\bar{y}. \end{cases} \tag{3.10}$$

Solving the third equation of (3.10), we get

$$\bar{z}(\theta) = \bar{z}(0) e^{-\lambda\theta} \cdot e^{-\int_0^\theta (\mu + \delta_2 + k(\sigma)) d\sigma} = p\bar{y} \cdot e^{-\lambda\theta} \cdot \Pi(\theta). \tag{3.11}$$

Solving the first equation of (3.10), we get

$$\bar{x} = \frac{-\beta S^*}{\lambda + \mu + \beta U_1^*}\bar{y}. \tag{3.12}$$

Substituting (3.11) and (3.12) into the second equation of (3.10) and cancelling $\bar{y}$ (for $\bar{y} \neq 0$), we get

$$p\int_0^\infty k(\theta)e^{-\lambda\theta}\Pi(\theta)d\theta = \lambda + \mu + \delta_1 + p - \beta S^* \cdot \frac{\lambda + \mu}{\lambda + \mu + \beta U_1^*}. \tag{3.13}$$

We also have

$$1 = \frac{\beta S^* \cdot \dfrac{\lambda + \mu}{\lambda + \mu + \beta U_1^*}}{\lambda + \mu + \delta_1 + p - p\displaystyle\int_0^\infty k(\theta)e^{-\lambda\theta}\Pi(\theta)d\theta}. \tag{3.14}$$

If the real part $\mathrm{Re}\lambda \geq 0$, taking the absolute value of the right hand side (RHS) of (3.14) and using the formula in (2.9), we have

$$\begin{aligned}
|\mathrm{RHS}| &\leq \frac{\beta S^*\left|\dfrac{\lambda + \mu}{\lambda + \mu + \beta U_1^*}\right|}{\left|\lambda + \mu + \delta_1 + p - p\displaystyle\int_0^\infty k(\theta)e^{-\lambda\theta}\Pi(\theta)d\theta\right|} \\
&< \frac{\beta S^*}{\left|\mu + \delta_1 + p - p\displaystyle\int_0^\infty k(\theta)\Pi(\theta)d\theta\right|} \\
&= \frac{\beta S^*}{\mu + \delta_1 + p - pK} \\
&= 1.
\end{aligned}$$

This is impossible, implying that Eq.(3.14) cannot have a root with nonnegative real part. There we have shown that the unique drug spread equilibrium E^* is locally asymptotically stable if $\mathcal{R}_0 > 1$. This completes the proof of Theorem 3.3. $\square$

3.4 Uniform persistence

In order to define the invariant sets of the uniform persistence analysis, we define

$$\tilde{\mathcal{M}} := \mathbb{R}_+ \times \{0\} \times \hat{\mathcal{M}}, \qquad \partial\tilde{\mathcal{M}} := \mathcal{X}_{0+}\backslash\tilde{\mathcal{M}}. \tag{3.15}$$

Theorem 3.4 *$\partial\tilde{\mathcal{M}}$ is positively invariant under the semiflow $\{U(t)\}_{t\geq 0}$ generated by system (3.3) on $\mathcal{X}_{0+}$. Moreover, the drug-free equilibrium $E_0(S_0^*, 0, 0, 0_{L^1})$ is globally asymptotically stable for the semiflow $\{U(t)\}_{t\geq 0}$ restricted to $\partial\tilde{\mathcal{M}}$.*

Proof. Let $\big(S^0, U_1^0, 0, U_2^0(\cdot)\big) \in \partial\tilde{\mathcal{M}}$. Then $\big(U_1^0, U_2^0(\cdot)\big) \in \mathbb{R}_+ \times L_+^1\big((0,+\infty),\mathbb{R}\big) \setminus \hat{\mathcal{M}}$ and we have

$$\begin{cases} \dfrac{dU_1(t)}{dt} = \beta S(t)U_1(t) - \big(\mu+\delta_1+p\big)U_1(t) + \displaystyle\int_0^\infty k(\theta)U_2(\theta,t)d\theta, \\ \dfrac{\partial U_2(\theta,t)}{\partial\theta} + \dfrac{\partial U_2(\theta,t)}{\partial t} = -\big(\mu+\delta_2+k(\theta)\big)U_2(\theta,t), \\ U_2(0,t) = p\ U_1(t), \\ U_1(0) = 0, \quad U_2(\theta,0) = U_2^0(\theta). \end{cases} \tag{3.16}$$

Since $S(t) \le \dfrac{\Lambda}{\mu}$, it follows that

$$U_1(t) \le \hat{U}_1(t), \quad U_2(\theta,t) \le \hat{U}_2(\theta,t), \tag{3.17}$$

where

$$\begin{cases} \dfrac{d\hat{U}_1(t)}{dt} = \beta\dfrac{\Lambda}{\mu}\hat{U}_1(t) - \big(\mu+\delta_1+p\big)\hat{U}_1(t) + \displaystyle\int_0^\infty k(\theta)\hat{U}_2(\theta,t)d\theta, \\ \dfrac{\partial\hat{U}_2(\theta,t)}{\partial\theta} + \dfrac{\partial\hat{U}_2(\theta,t)}{\partial t} = -\big(\mu+\delta_2+k(\theta)\big)\hat{U}_2(\theta,t), \\ \hat{U}_2(0,t) = p\ \hat{U}_1(t), \\ \hat{U}_1(0) = 0, \quad \hat{U}_2(\theta,0) = U_2^0(\theta). \end{cases} \tag{3.18}$$

By use of Volterra formulation, we integrate along the characteristic lines $t-\theta = \text{const.}$ for all $t > 0$, and solve the terms $\hat{U}_2(\theta,t)$ as the following expressions:

$$\hat{U}_2(\theta,t) = \begin{cases} \hat{U}_2(t-\theta,0)\Pi(\theta) = p\hat{U}_1(t-\theta)\Pi(\theta), & t > \theta, \\ \hat{U}_2^0(\theta-t)\dfrac{\Pi(\theta)}{\Pi(\theta-t)}, & t < \theta. \end{cases} \tag{3.19}$$

Substituting the above expression into the first equation of (3.18) yields

$$\frac{d\hat{U}_1(t)}{dt} = \beta\frac{\Lambda}{\mu}\hat{U}_1(t) - \big(\mu+\delta_1+p\big)\hat{U}_1(t) + p\int_0^t k(\theta)\hat{U}_1(t-\theta)\Pi(\theta)d\theta + F(t), \tag{3.20}$$

where

$$F(t) = \int_t^\infty k(\theta)\hat{U}_1^0(\theta-t)\frac{\Pi(\theta)}{\Pi(\theta-t)}d\theta.$$

Since $\big(U_1^0, U_2^0(\cdot)\big) \in \mathbb{R}_+ \times L_+^1\big((0,+\infty),\mathbb{R}\big) \setminus \hat{\mathcal{M}}$ and $k(\theta) \in L_+^1\big((0,+\infty),\mathbb{R}\big) \setminus \{0_{L^\infty}\}$, we can deduce that $F(t) \equiv 0$ for all $t \ge 0$. Accordingly, the system

$$\begin{cases} \dfrac{d\hat{U}_1(t)}{dt} = \beta\dfrac{\Lambda}{\mu}\hat{U}_1(t) - \big(\mu+\delta_1+p\big)\hat{U}_1(t) + p\displaystyle\int_0^t k(\theta)\hat{U}_1(t-\theta)\Pi(\theta)d\theta \\ \hat{U}_1(0) = 0 \end{cases} \tag{3.21}$$

has a unique solution $\hat{U}_1(t) = 0$. Consequently, it follows from (3.19) that $\hat{U}_2(\theta, t) = 0$ for $0 \leq \theta \leq t$. For $t < \theta$, we have

$$\big\|\hat{U}_2(\theta,t)\big\|_{L^1} = \left\|\hat{U}_2^0(\theta-t)\frac{\Pi(\theta)}{\Pi(\theta-t)}\right\|_{L^1} \leq e^{-\mu t}\big\|U_2^0\big\|_{L^1},$$

which imply that $\hat{U}_2(\theta, t) \to 0$ as t tends to infinity. By using (3.17), we have $U_1(t) = 0$ and $U_2(\theta, t) \to 0$ as $t \to \infty$. It follows from the first equation of system (2.1) that $S(t) \to S^0$ as $t \to \infty$. Thus, the drug-free equilibrium E_0 is globally asymptotically stable in $\partial\tilde{\mathcal{M}}$. This completes the proof of Theorem 3.4. $\square$

Next, we introduce the following result about linear scalar Volterra integro-differential equations which will be helpful in next proofs.

Lemma 3.1([34]) *Consider the following scalar Volterra integro-differential equations:*

$$\frac{dh(t)}{dt} = \int_0^\infty \eta(\theta)h(t-\theta)d\theta - ah(t), \quad h(0) > 0,$$

where $\eta(\cdot) \in L^1_+(0, +\infty)$, and $\int_0^\infty \eta(\theta)d\theta > a$. There is a unique solution $h(t)$ which is unbounded.

Finally, by combining Theorem 4.2 in Hale and Waltman [35] and Theorem 3.7 in Magal and Zhao [36], we are able to prove the following theorem.

Theorem 3.5 *Assume that $\mathcal{R}_0 > 1$. Then the semiflow $\big\{U(t)\big\}_{t\geq 0}$ generated by system (3.3) is uniformly persistent in $\tilde{\mathcal{M}}$ with respect to the decomposition $(\partial\tilde{\mathcal{M}}, \tilde{\mathcal{M}})$, i.e., there exists $\varepsilon > 0$ which is independent of initial values such that for each $\big(S, U_1, 0, U_2^0\big) \in \tilde{\mathcal{M}}$,*

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

Furthermore, the semiflow $\big\{U(t)\big\}_{t\geq 0}$ has a compact global attractor $\mathcal{A}_0$ in $\tilde{\mathcal{M}}$.

Proof. Since the drug-free equilibrium $E_0\big(S_0^*, 0, 0, 0_{L^1}\big)$ is globally asymptotically stable in $\partial\tilde{\mathcal{M}}$, we need only to study the behavior of the solution starting in $\hat{\mathcal{M}}$ in some neighborhood of E_0. Note

$$W^s\big(\{E_0\}\big) = \Big\{x \in \mathcal{X}_{0+} : \lim_{t\to+\infty} U(t)x = E_0\Big\}.$$

We need only to show

$$W^s\big(\{E_0\}\big) \cap \tilde{\mathcal{M}} = \emptyset.$$

For the sake of contradiction, we assume that there exists a list of $x_n = \big(S^n(0), U_1^n(0), 0, U_2^n(\cdot, 0)\big) \in \big\{y \in \tilde{\mathcal{M}} : \|E_0 - y\| \leq \varsigma\big\}$ such that

$$\big\|E_0 - U(t)x_n\big\| \leq \frac{1}{n+1}, \quad \forall\, t \geq 0.$$

Set $\big(S^n(t), U_1^n(t), 0, U_2^n(\cdot,t)\big) := U(t)x_n$. Then for all $t \geq 0$, we have

$$\big\|\big(S^n(t), U_1^n(t), 0, U_2^n(\cdot,t)\big) - \big(S_0^*, 0, 0, 0_{L^1}\big)\big\| \leq \frac{1}{n+1}, \quad \forall\, t \geq 0.$$

Then we can choose large enough $n > 0$ such that $S_0^* - \frac{1}{n+1} > 0$. For the chosen n, there exists a $T > 0$ such that for all $t > T$ we have

$$S_0^* - \frac{1}{n+1} < S^n(t) < S_0^* + \frac{1}{n+1}, \quad 0 \leq U_1^n(t) \leq \frac{1}{n+1}.$$

From the solutions (3.1), we obtain

$$U_2(\theta,t) = U_2(t-\theta,0)\Pi(\theta) + U_2^0(\theta-t)\frac{\Pi(\theta)}{\Pi(\theta-t)} \geq p\; U_1(t-\theta)\Pi(\theta). \tag{3.22}$$

By inserting (3.22) into the second equation of (2.1) and applying a simple comparison principle, we have

$$U_1^n(t) \geq \tilde{U}_1^n(t), \tag{3.23}$$

where $\tilde{U}_1^n(t)$ is the solution of the following auxiliary system

$$\begin{cases} \dfrac{d\tilde{U}_1^n(t)}{dt} = p\displaystyle\int_0^\infty k(\theta)\Pi(\theta)\tilde{U}_1^n(t-\theta)d\theta - \left\{\big(\mu+\delta_1+p\big) - \beta\left(S_0^* - \dfrac{1}{n+1}\right)\right\}\tilde{U}_1^n(t), \\ \tilde{U}_1^n(0) = U_1^n(0) \geq 0. \end{cases} \tag{3.24}$$

Note that if $\tilde{U}_1^n(0) = 0$, then $\tilde{U}_1^n(t) > 0$. So without loss of generality, we can take $\tilde{U}_1^n(0) > 0$. Since

$$\mathcal{R}_0 = \frac{\beta \cdot \frac{\Lambda}{\mu}}{(\mu+\delta_1+p) - pK} > 1,$$

there exists $n \in \mathbb{R}_+$ large enough such that

$$\frac{\beta \cdot \left\{\frac{\Lambda}{\mu} - \frac{1}{n+1}\right\}}{(\mu+\delta_1+p) - pK} > 1.$$

Note $S_0^* = \dfrac{\Lambda}{\mu}$ and $K = \displaystyle\int_0^\infty k(\theta)\Pi(\theta)d\theta$. Therefore, we have

$$p\int_0^\infty k(\theta)\Pi(\theta)d\theta > \big(\mu+\delta_1+p\big) - \beta\left(S_0^* - \frac{1}{n+1}\right).$$

By Lemma 3.1, $\tilde{U}_1^n(t)$ is unbounded. Since $U_1^n(t) \geq \tilde{U}_1^n(t)$, we get that $U_1^n(t)$ is unbounded. This contradicts to the boundedness of $U_1^n(t)$. Thus, $W^s\big(\{E_0\}\big) \cap \tilde{\mathcal{M}} = \emptyset$ holds true.

From Theorem 3.1, it then follows that the semiflow $\big\{U(t)\big\}_{t\geq 0}$ is asymptotically smooth, point dissipative and that the forward trajectory of a bound set is bounded. Furthermore, the drug-free equilibrium E_0 is globally asymptotically stable in $\partial\tilde{\mathcal{M}}$. Thus, Theorem 4.2 of Hale and Waltman [35] implies the semiflow $\big\{U(t)\big\}_{t\geq 0}$ is uniformly persistent with respect to $(\partial\tilde{\mathcal{M}}, \tilde{\mathcal{M}})$. The proof of Theorem 3.5 is thus completed. $\square$

4 Proofs of the main results

In the previous section we established the local stability of the equilibria, that is, if the initial conditions are close enough to the equilibrium, the solution will converge to that equilibrium. Furthermore, we obtain the uniform persistence of the system (2.1). In this section our objective is to extend above local results to global results. That is, given the conditions on the parameters, convergence to the equilibrium occurs independently of the initial conditions.

4.1 Global stability of the drug-free equilibrium

As a first step, We will use Lyapunov functional method to establish the global stability of the drug-free equilibrium.

Proof of Theorem 2.2 From Theorem 3.2 we know that the drug-free equilibrium $E_0(S_0^*, 0, 0)$ of system (2.1) is locally asymptotically stable if $\mathcal{R}_0 < 1$. In the following, we only need to show that the drug-free equilibrium E_0 is the global attractor in $\mathbb{R}_+ \times \mathbb{R}_+ \times L_+\big((0,+\infty),\mathbb{R}\big)\backslash\partial\mathcal{M}_0$ if $\mathcal{R}_0 < 1$, i.e.,

$$\mathcal{A}_0 = \big\{E_0\big\}.$$

We will use a suitable Lyapunov functional to approach the problem. We adopt the logistic function used in [24]. Define

$$g(x) = x - 1 - \ln x, \quad x \in \mathbb{R}^+. \tag{4.1}$$

We note that $g(x) \geq 0$ for all $x > 0$. $g(x)$ achieves its global minimum at one, with $g(1) = 0$. Moreover, we also have

$$g'(x) = 1 - \frac{1}{x}.$$

This fact is widely used in the proofs of global stability.

For ease of presentation, let us define

$$\begin{aligned} \alpha(\theta) &= \int_\theta^\infty k(\sigma) \exp\left\{-\int_\theta^\sigma \Big(\mu + \delta_2 + k(\tau)\Big) d\tau\right\} d\sigma \\ &= \int_\theta^\infty k(\sigma) \frac{\Pi(\sigma)}{\Pi(\theta)} d\sigma. \end{aligned} \tag{4.2}$$

Note that $\alpha(\theta) > 0$ for all $0 < \theta < +\infty$. We can easily check that

$$\alpha(0) = \int_0^\infty k(\sigma)\Pi(\sigma)d\sigma = K. \tag{4.3}$$

We also have

$$\alpha'(\theta) = \alpha(\theta)\Big(\mu + \delta_2 + k(\theta)\Big) - k(\theta). \tag{4.4}$$

Now let us define the following Lyapunov functional

$$V(t) = V_1(t) + U_1(t) + V_2(t), \tag{4.5}$$

where

$$V_1(t) = S_0^* g\left(\frac{S(t)}{S_0^*}\right), \quad V_2(t) = \int_0^\infty \alpha(\theta) U_2(\theta, t) d\theta. \tag{4.6}$$

We can easily see that the function $V(t)$ is bounded when restricted to $\mathcal{A}_0$. Since the function $g(x)$ is nonnegative for all $x > 0$, and has the global minimum at $x = 1$, it then follows that the function $V(t)$ is nonnegative and the point E_0 is the global minimum point. We can also easily see that the function $V(t)$ is continuously differentiable.

First, calculating the time derivative of $V_1(t)$ along with the solution curves of system (2.1) and using the fact $\Lambda = \mu S_0^*$, we have

$$\begin{aligned} V_1'(t) &= S_0^* \left(1 - \frac{S_0^*}{S(t)}\right) \frac{S'(t)}{S_0^*} \\ &= S_0^* \left(\frac{1}{S_0^*} - \frac{1}{S(t)}\right) \Big(\Lambda - \beta S(t) U_1(t) - \mu S(t)\Big) \\ &= S_0^* \left(\frac{1}{S_0^*} - \frac{1}{S(t)}\right) \Big(\mu\big(S_0^* - S(t)\big) - \beta S(t) U_1(t)\Big) \\ &= -\frac{\big(S_0^* - S(t)\big)^2}{S(t)} + \beta S_0^* U_1(t) - \beta S(t) U_1(t). \end{aligned} \tag{4.7}$$

Next, calculating the time derivative of $V_2(t)$ along with the solution curves of system (2.1) and using (4.3),(4.4) and collecting terms, we obtain

$$\begin{aligned} V_2'(t) &= \int_0^\infty \alpha(\theta) \frac{\partial U_2(\theta, t)}{\partial t} d\theta \\ &= -\int_0^\infty \alpha(\theta) \frac{\partial U_2(\theta, t)}{\partial \theta} d\theta - \int_0^\infty \alpha(\theta) \Big(\mu + \delta_2 + k(\theta)\Big) U_2(\theta, t) d\theta \\ &= -\alpha(\theta) U_2(\theta, t)\Big|_{\theta=0}^{\theta=\infty} + \int_0^\infty U_2(\theta, t) \frac{\partial \alpha(\theta)}{\partial \theta} d\theta - \int_0^\infty \alpha(\theta) \Big(\mu + \delta_2 + k(\theta)\Big) U_2(\theta, t) d\theta \\ &= -\alpha(\theta) U_2(\theta, t)\Big|_{\theta=\infty} + \alpha(0) U_2(0, t) + \int_0^\infty U_2(\theta, t) \Big[\alpha(\theta)\Big(\mu + \delta_2 + k(\tau)\Big) - k(\theta)\Big] d\theta \\ &\quad - \int_0^\infty \alpha(\theta) \Big(\mu + \delta_2 + k(\theta)\Big) U_2(\theta, t) d\theta \\ &= -\alpha(\theta) U_2(\theta, t)\Big|_{\theta=\infty} + \alpha(0) U_2(0, t) - \int_0^\infty k(\theta) U_2(\theta, t) d\theta \\ &= -\alpha(\theta) U_2(\theta, t)\Big|_{\theta=\infty} + p U_1(t) \int_0^\infty k(\theta) \Pi(\theta) d\theta - \int_0^\infty k(\theta) U_2(\theta, t) d\theta. \end{aligned} \tag{4.8}$$

Note the formula of $\mathcal{R}_0$. Adding all three components of the Lyapunov functional, we have

$$\begin{aligned} V'(t) &= V_1'(t) + U_1'(t) + V_2'(t) \\ &= -\frac{\big(S_0^* - S(t)\big)^2}{S(t)} + \beta S_0^* U_1(t) - \big(\mu + \delta_1 + p\big)U_1(t) - \alpha(\theta)U_2(\theta,t)\Big|_{\theta=\infty} \\ &\quad + pU_1(t)\int_0^\infty k(\theta)\Pi(\theta)d\theta \\ &= -\frac{\big(S_0^* - S(t)\big)^2}{S(t)} + \left\{\big(\mu + \delta_1 + p\big) - p\int_0^\infty k(\theta)\Pi(\theta)d\theta\right\}\Big(\mathcal{R}_0 - 1\Big)U_1(t) \\ &\quad - \alpha(\theta)U_2(\theta,t)\Big|_{\theta=\infty} \\ &\leq 0. \end{aligned} \tag{4.9}$$

The last inequality follows from the fact that $\mathcal{R}_0 < 1$. Notice that $V'(t)$ equals zero if and only if $S(t) = S_0^*$ and $U_1(t) = 0$. We define a set

$$\Upsilon = \Big\{\big(S, U_1, U_2\big) \in \mathcal{S} \;\Big|\; V'(t) = 0\Big\}. \tag{4.10}$$

Thus, the set $\mathcal{A}_0 = \big\{E_0\big\}$ is the largest compact invariant set of Υ, i.e., this largest compact invariant set is the singleton given by the drug-free equilibrium. By the Lyapunov-LaSalle invariance principle[37], we conclude that the drug-free equilibrium E_0 is globally asymptotically stable when $\mathcal{R}_0 < 1$. This completes the proof of Theorem 2.2. $\square$

4.2 Global stability of the drug spread equilibrium

In the previous section, we have obtain that the system (2.1) is uniformly persistent and have a global attractor. Now we are ready to establish the global stability of the drug spread equilibrium E^*, i,e., for any initial condition, the solution of system (2.1) converges to E^* when $\mathcal{R}_0 > 1$. To demonstrate that with a suitable Lyapunov functional $W(t)$, we have to establish that $W'(t) \leq 0$ along the solution curves of system (2.1).

Proof of Theorem 2.3. The first result of Theorem 2.3 can be easily seen from Theorem 3.3, we need only to prove the second part. From Theorem 3.2 we know that the unique drug spread equilibrium $E^*(S^*, U_1^*, U_2^*(\theta)$ of system (2.1) is locally asymptotically stable if $\mathcal{R}_0 > 1$. In the following, we only need to show that the unique drug spread equilibrium E^* is the global attractor in $\mathbb{R}_+ \times \mathbb{R}_+ \times L_+\big((0,+\infty),\mathbb{R}\big)\backslash\partial\mathcal{M}_0$, i.e.,

$$\mathcal{A}_0 = \big\{E^*\big\}.$$

Similarly to the proof of Theorem 2.2, we still use a suitable Lyapunov functional to approach the problem.

Let $u(t) = (S(t); U_1(t); U_2(\theta; t))$ ba a complete solution to system (2.1) that lies in the attractor $\mathcal{A}_0$. From Theorem 3.5, we know there exist $\delta_1; \delta_2 > 0$ such that

$$\delta_1 \leq \frac{S(t)}{S^*} \leq \delta_2, \quad \delta_1 \leq \frac{U_1(t)}{U_1^*} \leq \delta_2, \quad \delta_1 \leq \frac{U_2(\theta, t)}{U_2^*(\theta)} \leq \delta_2$$

for all $t \in \mathbb{R}$ and $\theta \geq 0$.

Now let us define the following Lyapunov functional:

$$W(t) = W_S(t) + W_1(t) + W_2(t), \tag{4.11}$$

where

$$W_S(t) = S^* g\left(\frac{S(t)}{S^*}\right), \; W_1(t) = U_1^* g\left(\frac{U_1(t)}{U_1^*}\right), \; W_2(t) = \int_0^\infty \alpha(\theta) U_2^*(\theta) g\left(\frac{U_2(\theta, t)}{U_2^*(\theta)}\right) d\theta, \tag{4.12}$$

where $g(x) = x - 1 - \ln x$ $(x \in \mathbb{R}^+)$ is showed in (4.1) and $\alpha(\theta)$ is showed in (4.2). We can easily see that the function $W(t)$ is bounded when restricted to $\mathcal{A}_0$. Since the function $g(x)$ is nonnegative for all $x > 0$, and has the global minimum at $x = 1$, it then follows that the function $W(t)$ is nonnegative and the point E^* is the global minimum point. We can also easily see that the function $W(t)$ is continuously differentiable.

Because of the complexity of the expressions, we take the derivative of each component of the Lyapunov functional separately.

First, differentiating $W_S(t)$ along the solution curves of system (2.1) and using the fact $\Lambda = \beta S^* U_1^* + \mu S^*$, we have

$$\begin{aligned} W_S'(t) &= S^* \left(1 - \frac{S^*}{S(t)}\right) \frac{1}{S^*} S'(t) \\ &= S^* \left(\frac{1}{S^*} - \frac{1}{S(t)}\right) \Big(\Lambda - \beta S(t) U_1(t) - \mu S(t)\Big) \\ &= S^* \left(\frac{1}{S^*} - \frac{1}{S(t)}\right) \Big[\mu\big(S^* - S(t)\big) + \big(\beta S^* U_1^* - \beta S(t) U_1(t)\big)\Big] \\ &= -\frac{\mu(S(t) - S^*)^2}{S} + \beta S^* U_1^* \left(1 - \frac{S^*}{S(t)}\right) \left(1 - \frac{S(t)}{S^*} \frac{U_1(t)}{U_1^*}\right). \end{aligned} \tag{4.13}$$

Next, differentiating $W_1(t)$ along the solution curves of system (2.1), we have

$$\begin{aligned} W_1'(t) &= U_1^* \left(1 - \frac{U_1^*}{U_1(t)}\right) \frac{1}{U_1^*} U_1'(t) \\ &= U_1^* \left(\frac{1}{U_1^*} - \frac{1}{U_1(t)}\right) \left\{\beta S(t) U_1(t) - \big(\mu + \delta_1 + p\big) U_1(t) + \int_0^\infty k(\theta) U_2(\theta, t) d\theta\right\}. \end{aligned}$$

Note that

$$\mu+\delta_1+p=\frac{1}{U_1^*}\left(\beta S^*U_1^*+\int_0^\infty k(\theta)U_2^*(\theta)d\theta\right).$$

So we have

$$\begin{aligned}
&W_1'(t)\\
&=U_1^*\left(\frac{1}{U_1^*}-\frac{1}{U_1(t)}\right)\left\{\beta S(t)U_1(t)-\frac{U_1(t)}{U_1^*}\left(\beta S^*U_1^*+\int_0^\infty k(\theta)U_2^*(\theta)d\theta\right)\right.\\
&\quad\left.+\int_0^\infty k(\theta)U_2(\theta,t)d\theta\right\}\\
&=\left(1-\frac{U_1^*}{U_1(t)}\right)\left\{\beta S^*U_1^*\left(\frac{S(t)}{S^*}\frac{U_1(t)}{U_1^*}-\frac{U_1(t)}{U_1^*}\right)\right.\\
&\quad\left.+\int_0^\infty k(\theta)U_2^*(\theta)\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}-\frac{U_1(t)}{U_1^*}\right)d\theta\right\}\\
&=\beta S(t)U_1(t)-\beta S^*U_1(t)-\beta S(t)U_1^*+\beta S^*U_1^*\\
&\quad+\int_0^\infty k(\theta)U_2^*(\theta)\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}-\frac{U_1(t)}{U_1^*}-\frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)}+1\right)d\theta.
\end{aligned}\tag{4.14}$$

Now we turn to the derivative of $W_2(t)$.

$$\begin{aligned}
&W_2'(t)\\
&=\int_0^\infty \alpha(\theta)U_2^*(\theta)\cdot\frac{\partial}{\partial t}g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)d\theta\\
&=\int_0^\infty \alpha(\theta)U_2^*(\theta)\cdot\left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\frac{1}{U_2^*(\theta)}\frac{\partial U_2(\theta,t)}{\partial t}d\theta\\
&=\int_0^\infty \alpha(\theta)U_2^*(\theta)\cdot\left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\frac{1}{U_2^*(\theta)}\left\{-\frac{\partial U_2(\theta,t)}{\partial\theta}-\big(\mu+\delta_2+k(\theta)\big)U_2(\theta,t)\right\}d\theta\\
&=-\int_0^\infty \alpha(\theta)U_2^*(\theta)\cdot\left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\frac{U_2(\theta,t)}{U_2^*(\theta)}\left\{\frac{U_{2\theta}(\theta,t)}{U_2(\theta,t)}+\big(\mu+\delta_2+k(\theta)\big)\right\}d\theta\\
&=-\int_0^\infty \alpha(\theta)U_2^*(\theta)\cdot\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}-1\right)\left\{\frac{U_{2\theta}(\theta,t)}{U_2(\theta,t)}+\big(\mu+\delta_2+k(\theta)\big)\right\}d\theta.
\end{aligned}\tag{4.15}$$

where $U_{2\theta}(\theta,t)$ denotes $\dfrac{\partial U_2(\theta,t)}{\partial\theta}$.

Note that

$$\begin{aligned}
\frac{\partial}{\partial\theta}g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right) &= \left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\cdot\frac{\partial}{\partial\theta}\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\\
&= \left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\cdot\frac{\frac{\partial U_2(\theta,t)}{\partial\theta}U_2^*(\theta)-U_2(\theta,t)\frac{dU_2^*(\theta)}{d\theta}}{\big(U_2^*(\theta)\big)^2}\\
&= \left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\cdot\frac{U_{2\theta}(\theta,t)U_2^*(\theta)-U_2(\theta,t)\big[-\big(\mu+\delta_2+k(\theta)\big)U_2^*(\theta)\big]}{\big(U_2^*(\theta)\big)^2}\\
&= \left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\cdot\frac{U_{2\theta}(\theta,t)+U_2(\theta,t)\big(\mu+\delta_2+k(\theta)\big)}{U_2^*(\theta)}\\
&= \left(1-\frac{U_2^*(\theta)}{U_2(\theta,t)}\right)\cdot\frac{U_2(\theta,t)}{U_2^*(\theta)}\left\{\frac{U_{2\theta}(\theta,t)}{U_2(\theta,t)}+\big(\mu+\delta_2+k(\theta)\big)\right\}\\
&= \left(\frac{U_2(\theta,t)}{U_2^*(\theta)}-1\right)\cdot\left\{\frac{U_{2\theta}(\theta,t)}{U_2(\theta,t)}+\big(\mu+\delta_2+k(\theta)\big)\right\}.
\end{aligned} \tag{4.16}$$

Substituting (4.16) into (4.15) and using integration by parts, we obtain

$$\begin{aligned}
W_2'(t) &= -\int_0^\infty \alpha(\theta)U_2^*(\theta)\cdot\frac{\partial}{\partial\theta}g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)d\theta\\
&= -\alpha(\theta)U_2^*(\theta)g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=0}^{\theta=\infty}+\int_0^\infty g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\frac{d}{d\theta}\Big(\alpha(\theta)U_2^*(\theta)\Big)d\theta\\
&= -\alpha(\theta)U_2^*(\theta)g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=\infty}+\alpha(0)U_2^*(0)g\left(\frac{U_2(0,t)}{U_2^*(0)}\right)\\
&\quad+\int_0^\infty g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\frac{d}{d\theta}\Big(\alpha(\theta)U_2^*(\theta)\Big)d\theta.
\end{aligned} \tag{4.17}$$

Note that

$$\begin{aligned}
\frac{d}{d\theta}\Big(\alpha(\theta)U_2^*(\theta)\Big) &= \frac{d}{d\theta}\alpha(\theta)\cdot U_2^*(\theta)+\alpha(\theta)\cdot\frac{d}{d\theta}U_2^*(\theta)\\
&= \Big[\alpha(\theta)\Big(\mu+\delta_2+k(\theta)\Big)-k(\theta)\Big]\cdot U_2^*(\theta)+\alpha(\theta)\cdot\Big[-\Big(\mu+\delta_2+k(\theta)\Big)U_2^*(\theta)\Big]\\
&= -k(\theta)U_2^*(\theta),
\end{aligned} \tag{4.18}$$

and

$$\alpha(0)=\int_0^\infty k(\theta)\Pi(\theta)d\theta,\quad U_2^*(0)=pU_1^*,\quad U_2(\theta,t)=pU_1(t). \tag{4.19}$$

Substituting (4.18) and (4.19) into (4.17), we also have

$$\begin{aligned} W_2'(t) &= -\alpha(\theta)U_2^*(\theta)\cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=\infty} + pU_1^*\int_0^\infty k(\theta)\Pi(\theta)d\theta\cdot g\left(\frac{U_1(t)}{U_1^*}\right) \\ &\quad - \int_0^\infty g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)k(\theta)U_2^*(\theta)d\theta. \end{aligned} \tag{4.20}$$

Combing the above three components of the Lyapunov function, we obtain

$$\begin{aligned} W'(t) &= W_S'(t) + W_1'(t) + W_2'(t) \\ &= \left\{-\frac{\mu\big(S(t)-S^*\big)^2}{S(t)} + \beta S^*U_1^*\left(1-\frac{S^*}{S(t)}\right)\left(1-\frac{S(t)}{S^*}\frac{U_1(t)}{U_1^*}\right)\right\} \\ &\quad +\Big\{\beta S(t)U_1(t) - \beta S^*U_1(t) - \beta S(t)U_1^* + \beta S^*U_1^* \\ &\quad + \int_0^\infty k(\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\Big\} \\ &\quad +\Big\{ -\alpha(\theta)U_2^*(\theta)\cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=\infty} + pU_1^*\int_0^\infty k(\theta)\Pi(\theta)d\theta\cdot g\left(\frac{U_1(t)}{U_1^*}\right) \\ &\quad - \int_0^\infty g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)k(\theta)U_2^*(\theta)d\theta\Big\} \\ &= -\frac{\mu\big(S(t)-S^*\big)^2}{S(t)} + \beta S^*U_1^*\left(1-\frac{S(t)}{S^*}\frac{U_1(t)}{U_1^*} - \frac{S^*}{S(t)} + \frac{U_1(t)}{U_1^*}\right) \\ &\quad +\beta S(t)U_1(t) - \beta S^*U_1(t) - \beta S(t)U_1^* + \beta S^*U_1^* \\ &\quad + \int_0^\infty k(\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 \\ &\quad -\alpha(\theta)U_2^*(\theta)\cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=\infty} + pU_1^*\int_0^\infty k(\theta)\Pi(\theta)d\theta\cdot g\left(\frac{U_1(t)}{U_1^*}\right) \\ &\quad - \int_0^\infty k(\theta)U_2^*(\theta)\left(\frac{U_2(\theta,t)}{U_2^*(\theta)} - 1 - \ln\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)d\theta \\ &= -\frac{\mu\big(S(t)-S^*\big)^2}{S(t)} + \beta S^*U_1^*\left(2-\frac{S^*}{S(t)} - \frac{S(t)}{S^*}\right) \\ &\quad + \int_0^\infty k(\theta)U_2^*(\theta)\Big\{ - \frac{U_1(t)}{U_1^*} - \frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)} + 2 + \ln\frac{U_2(\theta,t)}{U_2^*(\theta)}\Big\}d\theta \\ &\quad -\alpha(\theta)U_2^*(\theta)\cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Big|_{\theta=\infty} + pU_1^*\int_0^\infty k(\theta)\Pi(\theta)d\theta\cdot g\left(\frac{U_1(t)}{U_1^*}\right). \end{aligned} \tag{4.21}$$

Rearranging equation (4.21), we can obtain

$$\begin{aligned} W'(t) &= -\frac{\mu\big(S(t)-S^*\big)^2}{S(t)} + \beta S^* U_1^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*}\right) \\ &\quad + \int_0^\infty k(\theta) U_2^*(\theta) \Bigg\{ \left(1 - \frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)} + \ln \frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)}\right) \\ &\quad + \left(1 - \frac{U_1(t)}{U_1^*} + \ln \frac{U_1(t)}{U_1^*}\right) \Bigg\} d\theta - \alpha(\theta) U_2^*(\theta) \cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Bigg|_{\theta=\infty} \\ &\quad + pU_1^* \int_0^\infty k(\theta)\Pi(\theta) d\theta \cdot g\left(\frac{U_1(t)}{U_1^*}\right) \qquad (4.22) \\ &= -\frac{\mu\big(S(t)-S^*\big)^2}{S(t)} + \beta S^* U_1^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*}\right) \\ &\quad - \int_0^\infty k(\theta) U_2^*(\theta) g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)}\right) - \int_0^\infty k(\theta) U_2^*(\theta) g\left(\frac{U_1(t)}{U_1^*}\right) d\theta \\ &\quad - \alpha(\theta) U_2^*(\theta) \cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Bigg|_{\theta=\infty} + pU_1^* \int_0^\infty k(\theta)\Pi(\theta) d\theta \cdot g\left(\frac{U_1(t)}{U_1^*}\right). \end{aligned}$$

Noticing the formula in (2.7), we have

$$\begin{aligned} W'(t) &= -\frac{\mu\big(S(t)-S^*\big)^2}{S(t)} + \beta S^* U_1^* \left(2 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*}\right) \\ &\quad - \int_0^\infty k(\theta) U_2^*(\theta) g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)}\right) - \int_0^\infty k(\theta) \cdot pU_1^*\Pi(\theta) \cdot g\left(\frac{U_1(t)}{U_1^*}\right) d\theta \\ &\quad - \alpha(\theta) U_2^*(\theta) \cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Bigg|_{\theta=\infty} + pU_1^* \int_0^\infty k(\theta)\Pi(\theta) d\theta \cdot g\left(\frac{U_1(t)}{U_1^*}\right) \qquad (4.23) \\ &= -\frac{\mu\big(S(t)-S^*\big)^2}{S(t)} - \beta S^* U_1^* \left(\frac{S^*}{S(t)} - 2 + \frac{S(t)}{S^*}\right) \\ &\quad - \int_0^\infty k(\theta) U_2^*(\theta) g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)}\right) - \alpha(\theta) U_2^*(\theta) \cdot g\left(\frac{U_2(\theta,t)}{U_2^*(\theta)}\right)\Bigg|_{\theta=\infty}. \end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean, we have

$$\frac{S^*}{S(t)} - 2 + \frac{S(t)}{S^*} \geq 0.$$

Hence, we have $W'(t) \leq 0$. Let

$$\widehat{\Upsilon} = \Big\{ \big(S, U_1, U_2\big) \in \mathcal{S} \;\Big|\; W'(t) = 0 \Big\}. \qquad (4.24)$$

We want to show that the largest invariant set in $\widehat{\Upsilon}$ is the singleton $\big\{E^*\big\}$. First, we notice that equality in (4.23) occurs if and only if $S(t) = S^*$, and

$$\frac{S^*}{S(t)} = \frac{S(t)}{S^*}, \quad \frac{U_1^*}{U_1(t)}\frac{U_2(\theta,t)}{U_2^*(\theta)} = 1 \quad \text{and} \quad \frac{U_2(\theta,t)}{U_2^*(\theta)} = 1. \qquad (4.25)$$

From conditions (4.25) it follows that

$$S(t) = S^*, \quad U_1(t) = U_1^*, \quad U_2(\theta, t) = U_2^*(\theta). \tag{4.26}$$

Thus, we conclude that the set $\mathcal{A}_0 = \left\{E^*\right\}$ is the largest compact invariant set of $\widehat{\Upsilon}$, i.e., this largest compact invariant set is the singleton given by the drug spread equilibrium. By the Lyapunov-LaSalle invariance principle[37], we conclude that the drug spread equilibrium E^* is globally asymptotically stable when $\mathcal{R}_0 > 1$. This completes the proof of Theorem 2.3. □

5 Discussion

Recently, several mathematical models (as mentioned in introduction) have been developed to describe the heroin epidemic. Most of these heroin epidemic models are ODE models and assume that the relapse rate are indifferent to the treat-age. In this paper, we present a heroin epidemic model with treat-age, based on the principles of mathematical epidemiology. The model accounts for relapse rate that depend on how long the host has been in treatment. We analyze the existence and stability of the equilibria of the model. We characterize the threshold conditions of the heroin epidemic model with an explicit formula for the reproduction number of heroin use, which gives the number of secondary untreated users that one untreated user will cause in an entirely susceptible population. The reproduction number is the threshold which completely determines the stability of the equilibria. By using the direct Lyapunov method and constructing appropriate Lyapunov functional, we show that the drug-free equilibrium is globally stable in the feasible region and the drug phenomenon always disappears if $\mathcal{R}_0 < 1$. If $\mathcal{R}_0 > 1$, the drug-free equilibrium is unstable and a unique drug spread equilibrium is globally asymptotically stable in the interior of the feasible region and the drug phenomenon will persist at the drug spread equilibrium if it is initially present.

Because the age-structured model in this paper is described by partial differential equations and the tools used for the ODE models can not be used for analyzing the dynamics of PDE models, it is difficult to analyze the dynamics, particularly the global stability, of the PDE models due to the lack of applicable theories. The method of Lyapunov functions is most commonly used to prove the global stability of nonlinear dynamical systems. In this paper, by constructed a class of global Lyapunov functionals, and proved that the dynamics of the heroin epidemic model are completely determined by the basic reproduction number. Lyapunov functions of this type has been widely used for analyzing the ODE models in the literature and was recently rediscovered (e.g., 24, 33, 38) to study the global stability of endemic equilibrium for the epidemic models with age of infection. But the techniques used for

the PDE models are quite different from the techniques used for the ODE models. Furthermore, since our heroin epidemic model exhibits the relapse phenomenon, the process that we prove the global stability of our age-structured model is not the trivial extension.

The reproduction number $\mathcal{R}_0$ is an increasing function of transmission coefficient β which gives the rate of becoming a drug user, but a decreasing function of p which is the rate of drug users who enter treatment. Our mathematical analysis suggests that the spread of the heroin use should be controlled through stringent screening measures to reduce the values of β, through educational campaigns at all social levels, and particularly to epidemiologists and treatment providers in order to increase the values of p. Furthermore, we have

$$\frac{\partial \mathcal{R}_0}{\partial K} = \frac{\beta \frac{\Lambda}{\mu} p}{[(\mu + \delta_1 + p) - pK]^2},$$

which signifies that as K increases, $\mathcal{R}_0$ increases. Since K is the probability of leaving the treatment class and then entering the untreated class, then long time treatment is beneficial to control the spread of habitual drug use.

For practical purposes, these results suggest that prevention is better than treatment. Efforts to increase prevention are more effective in controlling the spread of habitual heroin use than efforts to increase the number of individuals who have access to treatment. These results are provided with intention to inform and assist policy-makers in targeting prevention and treatment resources for maximum effectiveness.

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