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GLOBAL STABILITY FOR A HEROIN MODEL WITH AGE-DEPENDENT SUSCEPTIBILITY *

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Abstract In this paper, we consider global asymptotic properties for an age-structured model of heroin use based on the principles of mathematical epidemiology where the incidence rate depends on the age of susceptible individuals. The basic reproduction number of the heroin spread is obtained. It completely determines the stability of equilibria. Using the direct Lyapunov method with Volterra type Lyapunov function, we show that the drug-free equilibrium is globally asymptotically stable if the basic reproduction number is less than one, and the unique drug spread equilibrium is globally asymptotically stable if the basic reproduction number is greater than one.

Keywords Heroin model, age-structured, basic reproduction number, equilibrium, global stability.

1 Introduction

It's well-known that Heroin is an opiate drug that is synthesized from morphine[1]. Compared to morphine, heroin is more soluble in the fat cells. 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[2]. Heroin users

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are at high risk for addiction. It is estimated that about 23 percent of individuals who use heroin become dependent on it. Over the past two decades, China has faced a dramatic increase in illicit drug abuse accompanying rapid economic reform and development[3]. 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)[4, 5]. The spread of heroin habituation and addiction presents many of the well-known phenomena of epidemics, including rapid diffusion and clear geographic boundaries[6–8]. Statistical information for drug abuse, including heroin abuse, is given by various governmental agencies, one of which is the National Institute on Drug Abuse in the US. Mathematical modelling not only is a means that provides a predictive tool for how classes of drug users behave but also plays important role in understanding and combating drug addiction problems, and as such, could hopefully become a useful device to aid specialist teams in devising treatment strategies.

Recently, some mathematical models have been developed to describe the heroin epidemic (such as [9]-[14]). In these models, the population is divided 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. The authors in [9, 10] consider a susceptible-untreated users-treated users model with standard incidence rate and show that the steady states of the model are stable. Wang et al. in [11] uses mass action incidence rate and proves that the drug-free equilibrium and the unique endemic equilibrium are globally asymptotically stable under some conditions. Samanta in [12] considers a nonautonomous heroin epidemic model with time delay. [13, 14] investigate the global stability for heroin epidemic model with distributed delay.

However, all these studies assume that all individuals have the same level of susceptibility. In fact, the individuals with different age may have different level of susceptibility. The susceptibility of individuals varies significantly during their life time. These variations are firstly due to the development of the immune system. The individual level of susceptibility can also change following changes in the life style. The age-varying susceptibility is particularly apparent for some phenomena, such as heroin use or sexually transmitted diseases. For these 'infections', the probability of being infected directly depends on the number of contacts, and hence on the life style, which significantly varies with age. Moreover, studies, such as Elvebac et al. in [15], suggest that disease transmission models with age-dependent contact rates are more realistic than those that do not consider age-dependent contact rates. To address the need to involve age in heroin studies, in this paper, we present a heroin epidemic model with age-dependent susceptibility, based on the principles of mathematical epidemiology. The model incorporates an incidence rate that depends on the age of the susceptible individuals. We analyze the existence and stability of the equilibria of the model. It is shown that the existence and global asymptotical stability of equilibria is completely determined by the basic reproduction number. We use a suitable Lyapunov function to determine the global asymptotic stability of the equilibria for the age-structured model.

The paper is organized as follows. Our heroin epidemic model with age-dependent sus-

ceptibility is formulated in Section 2. The existence of a unique drug spread equilibrium is also established in this section. The global asymptotic stability of the drug-free equilibrium and drug spread equilibrium are investigated in Section 3 by the use of a suitable Lyapnuov function. Finally in section 4 we summarize our results.

2 The Model

On the premise that drug use follows a process that can be modelled in a similar way to the modelling of disease [16, 17], a mathematical 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, the process being modelled. Information from the ROSIE study [18] and feedback from professionals in addiction-related areas were fundamental in developing the model. In order to investigate the influence of the 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 $S(t,a), U_1(t)$ and $U_2(t)$, respectively. In particular, we assume that the distribution of the susceptibles with respect to age a at time t is $S(t,a)$ and that the susceptibility depends on the age a and this dependence is given by $\beta(a)$. Motivated by [9, 13], we formulate the heroin epidemic model with age-dependent susceptibility as the following set of equations:

$$\begin{cases} S(t,0) = \Lambda, \\ \dfrac{\partial S(t,a)}{\partial t} + \dfrac{\partial S(t,a)}{\partial a} = -\beta(a)S(t,a)U_1(t) - \mu S(t,a), \\ \dfrac{dU_1(t)}{dt} = \displaystyle\int_0^\infty \beta(a)U_1(t)S(t,a)da + kU_2(t) - (\mu + \delta_1 + p)U_1(t), \\ \dfrac{dU_2(t)}{dt} = pU_1(t) - (\mu + \delta_2 + k)U_2(t). \end{cases} \tag{1}$$

This system is equipped with the following initial conditions:

$$S(0,a) = \varphi(a), \quad U_1(0) = U_1^0, \quad U_2(0) = U_2^0. \tag{2}$$

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

♦ $S(t,a)$: the number of susceptible individuals with age a at time t in the population;

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

♦ $U_2(t)$: the number of drug users in treatment;

♦ Λ: the number per unit of time of individuals in the general population entering the susceptible population;

♦ $\beta(a)$: the rate of becoming a drug user at age a;

♦ 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: the probability of a drug user in treatment relapsing to untreated use;

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

All parameters are nonnegative, $\Lambda > 0$, and $\mu > 0$. We let $[a_1, a_2]$ be the age-interval of heroin users, i.e., an individual with the age outside that interval can not use heroin. We make the following assumptions on the parameter-functions.

Assumption 2.1 *The parameter-functions satisfy:*

1. *The function $\beta(a)$ is bounded and uniformly continuous. When of compact support, the support has non-zero Lebesgue measure, and $\beta(a) = 0$, if $a \notin [a_1, a_2]$.*
2. *The function $\varphi(a)$ is integrable.*

Define the space of functions

$$X = L^1(0, \infty) \times \mathbb{R} \times \mathbb{R}.$$

By the standard theory of functional differential equation[19], it can be verified that the system (1) with initial conditions (2) that belong to the positive cone X_+ has a unique solution $(S(t, a), U_1(t), U_2(t))$ which remains non-negative for all $t \geq 0$. Moreover, we can show the solutions of system (1) are ultimately uniformly bounded in X_+. To see that fact, we add all equations of system (1) and we have

$$\frac{d}{dt}\left(\int_0^\infty S(t,a)da + U_1(t) + U_2(t)\right) \leq \Lambda - \mu\left(\int_0^\infty S(t,a)da + U_1(t) + U_2(t)\right).$$

Hence,

$$\limsup_t \left(\int_0^\infty S(t,a)da + U_1(t) + U_2(t)\right) \leq \frac{\Lambda}{\mu}.$$

Therefore, the following set is positively invariant for system (1):

$$\Omega = \left\{(S, U_1, U_2) \in X_+ \mid \int_0^\infty S(t,a)da + U_1(t) + U_2(t) \leq \frac{\Lambda}{\mu}\right\}. \tag{3}$$

We introduce the reproduction number of the heroin epidemic model, which is given by the following expression:

$$\mathcal{R}_0 = \frac{\mu + \delta_2 + k}{(\mu + \delta_2 + k)(\mu + \delta_1) + (\mu + \delta_2)p} \int_0^\infty \beta(a) S_0^*(a) da, \tag{4}$$

where $S_0^*(a)$ is given in formula (9). To interpret formula (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 $\frac{k}{\mu+\delta_2+k}$ is the probability of surviving the drug users in treatment class, the total average time in the drug users not in treatment class (on multiple passes) is

$$\begin{aligned}&\frac{1}{\mu+\delta_1+p}\left[1+\frac{p}{\mu+\delta_1+p}\cdot\frac{k}{\mu+\delta_2+k}+\left(\frac{p}{\mu+\delta_1+p}\cdot\frac{k}{\mu+\delta_2+k}\right)^2+\cdots\right]\\&=\frac{\mu+\delta_2+k}{(\mu+\delta_2+k)(\mu+\delta_1)+(\mu+\delta_2)p}.\end{aligned}\tag{5}$$

Multiplying this by $\int_0^\infty \beta(a)S_0^*(a)da$ 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 [20]. Thus, $\mathcal{R}_0$ is the basic reproduction number. The basic reproduction number acts as a threshold as is shown in the following result.

Now we consider the steady states of system (1). The steady state $(S^*(a), U_1^*, U_2^*)$ of system (1) satisfies the equalities

$$\begin{cases}S^*(0)=\Lambda,\\ \dfrac{dS^*(a)}{da}=-\beta(a)S^*(a)U_1^*-\mu S^*(a),\\ 0=\displaystyle\int_0^\infty \beta(a)U_1^*S^*(a)da+kU_2^*-(\mu+\delta_1+p)U_1^*,\\ 0=pU_1^*-(\mu+\delta_2+k)U_2^*.\end{cases}\tag{6}$$

Solving the last equation of (6), we get

$$U_2^*=\frac{p}{\mu+\delta_2+k}U_1^*.\tag{7}$$

Substituting (7) into the third equation of (6), yields

$$0=U_1^*\int_0^\infty \beta(a)S^*(a)da+\left(\frac{kp}{\mu+\delta_2+k}-(\mu+\delta_1+p)\right)U_1^*.\tag{8}$$

If $U_1^*=0$, then we have $U_2^*=0$ from (7). From the first two equations of (6), we obtain

$$S_0^*(a)=S^*(0)e^{-\mu a}=\Lambda e^{-\mu a}.\tag{9}$$

Obviously, system (1) always has the drug-free equilibrium, in which there are no drug users present, given by

$$E_0=(S_0^*(a),0,0),\quad S_0^*(a)=\Lambda e^{-\mu a}.\tag{10}$$

If $U_1^*\neq 0$, then from (8), we have

$$0=\int_0^\infty \beta(a)S^*(a)da+\frac{kp}{\mu+\delta_2+k}-(\mu+\delta_1+p).\tag{11}$$

Additionally, solving the second equation of (6), we get

$$S^*(a)=S^*(0)e^{-\int_0^a(\mu+U_1^*\beta(\sigma))d\sigma}=\Lambda e^{-\int_0^a(\mu+U_1^*\beta(\sigma))d\sigma}.\tag{12}$$

Substituting (12) into (11), yields

$$0 = \int_0^\infty \beta(a) S_0^*(a) e^{-\int_0^a U_1^* \beta(\sigma) d\sigma} da + \frac{kp}{\mu + \delta_2 + k} - (\mu + \delta_1 + p). \tag{13}$$

We also have

$$\frac{\mu + \delta_2 + k}{(\mu + \delta_2 + k)(\mu + \delta_1) + (\mu + \delta_2)p} \int_0^\infty \beta(a) S_0^*(a) e^{-\int_0^a U_1^* \beta(\sigma) d\sigma} da = 1. \tag{14}$$

Consider the left-hand side of the last equality as a function of U_1^* and denote it by $F(U_1^*)$. It is easy to see that

$$F'(U_1^*) < 0, \quad \lim_{U_1^* \to +\infty} F(U_1^*) = 0, \quad \lim_{U_1^* \to -\infty} F(U_1^*) = +\infty, \quad F(0) = \mathcal{R}_0. \tag{15}$$

Therefore, equation (14) has a unique positive solution U_1^*. Hence, for all $\mathcal{R}_0 > 1$, there exist $S^*(a) = \Lambda e^{-\int_0^a (\mu + U_1^* \beta(\sigma)) d\sigma}$ and $U_1^* > 0$ (and $U_2^* = \dfrac{p}{\mu + \delta_2 + k} U_1^* > 0$), which satisfies (6). So we have the following result.

Theorem 2.1 *System (1) always has the drug-free equilibrium $E_0(S_0^*(a), 0, 0)$. In addition, it also has a unique equilibrium with drug users present $E^*(S^*(a), U_1^*, U_2^*)$ if $\mathcal{R}_0 > 1$.*

The local properties of the equilibria for our age-structured heroin model can be obtained similarly by the method in [21]-[23], and bibliography therein, so we omit these here. In next section, we address global asymptotic stability of system (1) by constructing appropriate Volterra type Lyapunov functions.

3 Global stability of the equilibria

In this section our objective is to obtain the global results of system (1). That is, given the conditions on the parameters, convergence to the equilibrium occurs independently of the initial conditions. Next, we address global asymptotic stability of system (1) by constructing appropriate Volterra type Lyapunov functions.

3.1 Global stability of the drug-free equilibrium

As a first step, we establish the global stability of the drug-free equilibrium. We will use Lyapunov function to approach the problem.

Theorem 3.1 *Assume $\mathcal{R}_0 \leq 1$. Then the drug-free equilibrium E_0 is globally asymptotically stable.*

Proof We will use a suitable Lyapunov function to approach the problem. We adopt the Volterra type Lyapunov function used in [24]-[27]. Define

$$g(x) = x - 1 - \ln x, \quad x \in \mathbb{R}^+. \tag{16}$$

We note that $g(x)$ is positive-definite for all $x > 0$, i.e., $g(x) \geq 0$ for all $x > 0$. And $g(x)$ achieves its unique 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.

Now we consider the following Lyapunov functional

$$V(t) = \int_0^\infty S_0^*(a) g\left(\frac{S(t,a)}{S_0^*(a)}\right) da + U_1(t) + \frac{k}{\mu+k+\delta_2} U_2(t). \tag{17}$$

Note that $V(S_0^*, 0, 0) = 0$. It is easy to see that the function is positive-definite and it is defined for all $S(t,a) > 0,\ U_1(t) > 0,\ U_2(t) > 0$, moreover, E_0 is the global minimum of the function.

Differentiating (17) along the solution curves of system (1), we have

$$\begin{aligned} V'(t) &= \int_0^\infty S_0^*(a)\left(\frac{1}{S_0^*(a)} - \frac{1}{S(t,a)}\right)\frac{\partial S(t,a)}{\partial t} da + \frac{dU_1(t)}{dt} + \frac{k}{\mu+k+\delta_2}\frac{dU_2(t)}{dt} \\ &= \int_0^\infty S_0^*(a)\left(\frac{1}{S_0^*(a)} - \frac{1}{S(t,a)}\right)\left(-\frac{\partial S(t,a)}{\partial a} - \mu S(t,a) - \beta(a)U_1(t)S(t,a)\right) da \\ &\quad + \left(\int_0^\infty \beta(a)U_1(t)S(t,a)da + kU_2(t) - \big(\mu+\delta_1+p\big)U_1(t)\right) \\ &\quad + \frac{k}{\mu+k+\delta_2}\Big[pU_1(t) - \big(\mu+\delta_2+k\big)U_2(t)\Big] \\ &= -\int_0^\infty S_0^*(a)\left(\frac{S(t,a)}{S_0^*(a)} - 1\right)\left(\frac{S_a(t,a)}{S(t,a)} + \mu + \beta(a)U_1(t)\right) da \\ &\quad + \int_0^\infty \beta(a)U_1(t)S(t,a)da - \big(\mu+\delta_1+p\big)U_1(t) + \frac{kp}{\mu+k+\delta_2}U_1(t). \end{aligned} \tag{18}$$

where $S_a(t,a)$ denotes $\dfrac{\partial S(t,a)}{\partial a}$. Note that

$$\frac{\partial}{\partial a} g\left(\frac{S(t,a)}{S_0^*(a)}\right) = \left(\frac{S(t,a)}{S_0^*(a)} - 1\right)\left(\frac{S_a(t,a)}{S(t,a)} + \mu\right). \tag{19}$$

Hence, using integration by parts, we get

$$\begin{aligned} &\int_0^\infty S_0^*(a)\left(\frac{S(t,a)}{S_0^*(a)} - 1\right)\left(\frac{S_a(t,a)}{S(t,a)} + \mu + \beta(a)U_1(t)\right) da \\ =\ &\int_0^\infty S_0^*(a)\left(\frac{S(t,a)}{S_0^*(a)} - 1\right)\left(\frac{S_a(t,a)}{S(t,a)} + \mu\right) da + \int_0^\infty S_0^*(a)\left(\frac{S(t,a)}{S_0^*(a)} - 1\right)\beta(a)U_1(t)da \\ =\ &\int_0^\infty S_0^*(a)\frac{\partial}{\partial a} g\left(\frac{S(t,a)}{S_0^*(a)}\right) da + \int_0^\infty \beta(a)U_1(t)\big(S(t,a) - S_0^*(a)\big)da \\ =\ &\left[S_0^*(a) g\left(\frac{S(t,a)}{S_0^*(a)}\right)\right]_{a=0}^{a=+\infty} - \int_0^\infty g\left(\frac{S(t,a)}{S_0^*(a)}\right)\frac{dS_0^*(a)}{da} da \\ &\quad + \int_0^\infty \beta(a)U_1(t)S(t,a)da - \int_0^\infty \beta(a)U_1(t)S_0^*(a)da. \end{aligned} \tag{20}$$

Note that

$$g\left(\frac{S(t,0)}{S_0^*(0)}\right) = g\left(\frac{\Lambda}{\Lambda}\right) = g(1) = 0, \quad \frac{d}{da}S_0^*(a) = -\mu S_0^*(a),$$

and the definition of $\mathcal{R}_0$ (see (4)), so we get

$$\begin{aligned} V'(t) &= -\left[S_0^*(a)g\left(\frac{S(t,a)}{S_0^*(a)}\right)\right]_{a=0}^{a=+\infty} + \int_0^\infty g\left(\frac{S(t,a)}{S_0^*(a)}\right)\frac{dS_0^*(a)}{da}da \\ &\quad + \int_0^\infty \beta(a)U_1(t)S_0^*(a)da - \big(\mu+\delta_1+p\big)U_1(t) + \frac{kp}{\mu+k+\delta_2}U_1(t) \\ &= -\left[S_0^*(a)g\left(\frac{S(t,a)}{S_0^*(a)}\right)\right]_{a=+\infty} + \int_0^\infty \big(-\mu S_0^*(a)\big)g\left(\frac{S(t,a)}{S_0^*(a)}\right)da \\ &\quad + \left\{\int_0^\infty \beta(a)S_0^*(a)da - \left[\big(\mu+\delta_1+p\big) - \frac{kp}{\mu+k+\delta_2}\right]\right\}U_1(t) \\ &= -\left[S_0^*(a)g\left(\frac{S(t,a)}{S_0^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \mu S_0^*(a)g\left(\frac{S(t,a)}{S_0^*(a)}\right)da \\ &\quad + \left[\big(\mu+\delta_1+p\big) - \frac{kp}{\mu+k+\delta_2}\right]\big(\mathcal{R}_0-1\big)U_1(t). \end{aligned} \tag{21}$$

Therefore, $\mathcal{R}_0 \le 1$ ensures that $V'(t) \le 0$ holds. Note that the strict equality holds only if $S(t,a) - S_0^*(a) = 0$. Obviously, $\Omega_0 = \{S(t,a) - S_0^*(a) = 0\} \subseteq \Omega$ is not an invariant subspace in the phase space $\Omega = (S, U_1, U_2)$: any trajectory, starting in $(S_0^*(a), U_1, U_2)$ with non-zero U_1 or U_2, leaves Ω_0, since non-zero $U_1(t)$ leads to growth of $U_2(t)$, and

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)\left(S(t,a) - S_0^*(a)\right) = \mu\left(S(t,a) - S_0^*(a)\right) - \beta(a)U_1(t)S(a) \neq 0. \tag{22}$$

That is, positive-definite function $V(t)$ has non-positive derivative $V'(t) \le 0$, and the only invariant subset, where $V'(t) = 0$ holds, is point $(S_0^*(a), 0, 0)$. Hence by Lyapunov-LaSalle asymptotic stability theorem [28, 29], $\mathcal{R}_0 \le 1$ ensures that the equilibrium $(S_0^*(a), 0, 0)$ is globally asymptotically stable. Therefore, we can conclude that the drug-free equilibrium is globally stable if $\mathcal{R}_0 \le 1$. This completes the proof.

3.2 Global stability of the drug spread equilibrium

Now we are ready to establish the global stability of the drug spread equilibrium E^*. To demonstrate that with a suitable Lyapunov function $W(t)$, we have to establish that $W'(t) \le 0$ along the solution curves of system (1). The following proposition summarizes the result.

Theorem 3.2 *Assume $\mathcal{R}_0 > 1$. Then, the drug spread equilibrium E^* is globally asymptotically stable.*

Proof We still use appropriate Volterra type Lyapunov function to approach the problem. With $g(x) = x - 1 - \ln x$ $(x \in \mathbb{R}^+)$, we take the Lyapunov function as follows

$$W(t) = \int_0^\infty S^*(a)\cdot g\left(\frac{S(t,a)}{S^*(a)}\right)da + U_1^*\cdot g\left(\frac{U_1(t)}{U_1^*}\right) + \frac{k}{\mu+\delta_2+k}U_2^*\cdot g\left(\frac{U_2(t)}{U_2^*}\right). \tag{23}$$

Note that $V(S^*(a), U_1^*, U_2^*) = 0$. It is easy to see that the function is positive-definite and it is defined for all $S(t,a) > 0,\ U_1(t) > 0,\ U_2(t) > 0$. Moreover, E^* is the global minimum of the function.

Differentiating (23) along the solution curves of system (1), we have

$$\begin{aligned}
W'(t) &= \int_0^\infty S^*(a)\left(\frac{1}{S^*(a)} - \frac{1}{S(t,a)}\right)\frac{\partial S(t,a)}{\partial t}da + U_1^*\left(\frac{1}{U_1^*} - \frac{1}{U_1(t)}\right)\frac{dU_1(t)}{dt} \\
&\quad + \frac{k}{\mu+\delta_2+k}U_2^*\left(\frac{1}{U_2^*} - \frac{1}{U_2(t)}\right)\frac{dU_2(t)}{dt} \\
&= \int_0^\infty S^*(a)\left(\frac{1}{S^*(a)} - \frac{1}{S(t,a)}\right)\left(-\frac{\partial S(t,a)}{\partial a} - \mu S(t,a) - \beta(a)U_1(t)S(t,a)\right)da \\
&\quad + U_1^*\left(\frac{1}{U_1^*} - \frac{1}{U_1(t)}\right)\left(\int_0^\infty \beta(a)U_1(t)S(t,a)da + kU_2(t) - \big(\mu+\delta_1+p\big)U_1(t)\right) \\
&\quad + \frac{k}{\mu+\delta_2+k}U_2^*\left(\frac{1}{U_2^*} - \frac{1}{U_2(t)}\right)\Big(pU_1(t) - \big(\mu+\delta_2+k\big)U_2(t)\Big) \\
&= -\int_0^\infty S^*(a)\left(\frac{S(t,a)}{S^*(a)} - 1\right)\left(\frac{S_a(t,a)}{S(t,a)} + \mu + \beta(a)U_1(t)\right)da \\
&\quad + \int_0^\infty \beta(a)U_1(t)S(t,a)da - \big(\mu+\delta_1+p\big)U_1(t) - \int_0^\infty \beta(a)U_1^*S(t,a)da \\
&\quad + \big(\mu+\delta_1+p\big)U_1^* - kU_1^*\frac{U_2(t)}{U_1(t)} + \frac{kp}{\mu+\delta_2+k}U_1(t) - \frac{kp}{\mu+\delta_2+k}U_2^*\frac{U_1(t)}{U_2(t)} + kU_2^*,
\end{aligned} \tag{24}$$

where $S_a(t,a)$ denotes $\dfrac{\partial}{\partial a}S(t,a)$. Note that

$$\frac{\partial}{\partial a}g\left(\frac{S(t,a)}{S^*(a)}\right) = \left(\frac{S(t,a)}{S^*(a)} - 1\right)\left(\frac{S_a(t,a)}{S(t,a)} + \mu + \beta(a)U_1^*\right), \tag{25}$$

$$\frac{d}{da}S^*(a) = -\mu S^*(a) - \beta(a)U_1^*S^*(a), \tag{26}$$

and

$$S(t,0) = S^*(0) = \Lambda. \tag{27}$$

Hence, using integration by parts, we obtain

$$\begin{aligned}
&\int_0^\infty S^*(a)\left(\frac{S(t,a)}{S^*(a)}-1\right)\left(\frac{S_a(t,a)}{S(t,a)}+\mu+\beta(a)U_1(t)\right)da\\
&=\int_0^\infty S^*(a)\left(\frac{S(t,a)}{S^*(a)}-1\right)\left(\frac{S_a(t,a)}{S(t,a)}+\mu+\beta(a)U_1^*\right)da\\
&\quad+\int_0^\infty S^*(a)\left(\frac{S(t,a)}{S^*(a)}-1\right)\beta(a)\big(U_1(t)-U_1^*\big)da\\
&=\int_0^\infty S^*(a)\frac{\partial}{\partial a}g\left(\frac{S(t,a)}{S^*(a)}\right)da+\int_0^\infty \beta(a)U_1(t)S(t,a)da-\int_0^\infty \beta(a)U_1^*S(t,a)da\\
&\quad-\int_0^\infty \beta(a)U_1(t)S^*(a)da+\int_0^\infty \beta(a)U_1^*S^*(a)da\\
&=\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=0}^{a=+\infty}-\int_0^\infty g\left(\frac{S(t,a)}{S^*(a)}\right)\frac{dS^*(a)}{da}da+\int_0^\infty \beta(a)U_1(t)S(t,a)da\\
&\quad-\int_0^\infty \beta(a)U_1^*S(t,a)da-\int_0^\infty \beta(a)U_1(t)S^*(a)da+\int_0^\infty \beta(a)U_1^*S^*(a)da\\
&=\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty}-\int_0^\infty \Big(-\mu S^*(a)-\beta(a)U_1^*S^*(a)\Big)g\left(\frac{S(t,a)}{S^*(a)}\right)da\\
&\quad+\int_0^\infty \beta(a)U_1(t)S(t,a)da-\int_0^\infty \beta(a)U_1^*S(t,a)da-\int_0^\infty \beta(a)U_1(t)S^*(a)da\\
&\quad+\int_0^\infty \beta(a)U_1^*S^*(a)da.
\end{aligned}\tag{28}$$

So we have

$$\begin{aligned}
W'(t) \quad &=-\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty}-\int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da\\
&\quad-\int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da+\int_0^\infty \beta(a)U_1(t)S^*(a)da\\
&\quad-\int_0^\infty \beta(a)U_1^*S^*(a)da-\big(\mu+\delta_1+p\big)U_1(t)+\big(\mu+\delta_1+p\big)U_1^*\\
&\quad-kU_1^*\frac{U_2(t)}{U_1(t)}+\frac{kp}{\mu+\delta_2+k}U_1(t)-\frac{kp}{\mu+\delta_2+k}U_2^*\frac{U_1(t)}{U_2(t)}+kU_2^*.
\end{aligned}\tag{29}$$

Notice that

$$\int_0^\infty \beta(a)U_1(t)S^*(a)da=\big(\mu+\delta_1+p\big)U_1(t)-\frac{kp}{\mu+\delta_2+k}U_1(t).\tag{30}$$

Substituting (30) into (29), we obtain

$$\begin{aligned} W'(t) &= -\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da \\ &\quad - \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da - \int_0^\infty \beta(a)U_1^*S^*(a)da \\ &\quad + \big(\mu+\delta_1+p\big)U_1^* - kU_1^*\frac{U_2(t)}{U_1(t)} - \frac{kp}{\mu+\delta_2+k}U_2^*\frac{U_1(t)}{U_2(t)} + kU_2^*. \end{aligned} \tag{31}$$

Since

$$\begin{aligned} &\big(\mu+\delta_1+p\big)U_1^* - kU_1^*\frac{U_2(t)}{U_1(t)} \\ &= \big(\mu+\delta_1+p\big)U_1^* + \left(\int_0^\infty \beta(a)U_1^*S^*(a)da - \big(\mu+\delta_1+p\big)U_1^*\right)\cdot\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*} \\ &= \big(\mu+\delta_1+p\big)U_1^*\left(1-\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right) + \int_0^\infty \beta(a)U_1^*S^*(a)\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}da \end{aligned} \tag{32}$$

and

$$\begin{aligned} kU_2^* - \frac{kp}{\mu+\delta_2+k}U_2^*\frac{U_1(t)}{U_2(t)} &= kU_2^* - k\cdot\frac{pU_1^*}{\mu+\delta_2+k}\cdot\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)} \\ &= kU_2^* - k\cdot U_2^*\cdot\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)} \\ &= kU_2^*\left(1-\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}\right). \end{aligned} \tag{33}$$

Substituting (32) and (33) into (31), we can simplify $W'(t)$ as follows

$$\begin{aligned} W'(t) &= -\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da \\ &\quad - \int_0^\infty \beta(a)U_1^*S^*(a)da - \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da \\ &\quad + \big(\mu+\delta_1+p\big)U_1^*\left(1-\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right) \\ &\quad + \int_0^\infty \beta(a)U_1^*S^*(a)\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}da + kU_2^*\left(1-\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}\right). \end{aligned} \tag{34}$$

Rearranging equation (34), we can obtain

$$
\begin{aligned}
W'(t) &= -\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da \\
&\quad - \int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da - \int_0^\infty \beta(a)U_1^*S^*(a)\left(1-\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)da \\
&\quad + \big(\mu+\delta_1+p\big)U_1^*\left(1-\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right) + kU_2^*\left(1-\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}\right) \\
&= -\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da \\
&\quad - \int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da + \int_0^\infty \beta(a)U_1^*S^*(a)\ln\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}da \\
&\quad - \int_0^\infty \beta(a)U_1^*S^*(a)\left(1-\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}+\ln\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)da \\
&\quad + \big(\mu+\delta_1+p\big)U_1^*\left[\left(1-\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}+\ln\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)-\ln\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right] \\
&\quad + kU_2^*\left(1-\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}+\ln\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}\right) - kU_2^*\ln\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)} \qquad (35) \\
&= -\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da \\
&\quad - \int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da + \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)da \\
&\quad - \big(\mu+\delta_1+p\big)U_1^*g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right) - kU_2^*g\left(\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}\right) \\
&\quad + \left(\int_0^\infty \beta(a)U_1^*S^*(a)da - \big(\mu+\delta_1+p\big)U_1^* + kU_2^*\right)\ln\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*} \\
&= -\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da \\
&\quad - \int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da + \int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)da \\
&\quad - \big(\mu+\delta_1+p\big)U_1^*g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right) - kU_2^*g\left(\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}\right).
\end{aligned}
$$

However

$$\begin{aligned}\int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)da &= \Big[\big(\mu+\delta_1+p\big)U_1^* - kU_2^*\Big]\cdot g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)\\ &= \big(\mu+\delta_1+p\big)U_1^* g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right)\\ &\quad -kU_2^* g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right).\end{aligned} \tag{36}$$

So equation (35) can be further reduced to

$$\begin{aligned}W'(t) &= -\left[S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)\right]_{a=+\infty} - \int_0^\infty \mu S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da\\ &\quad -\int_0^\infty \beta(a)U_1^*S^*(a)g\left(\frac{S(t,a)}{S^*(a)}\right)da - kU_2^*g\left(\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}\right)\\ &\quad -kU_2^*g\left(\frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}\right).\end{aligned} \tag{37}$$

Hence, $W'(t)\le 0$. Let

$$\widehat{\Upsilon} = \big\{(S,U_1,U_2)\in\Omega | W'(t)=0\big\}. \tag{38}$$

We want to show that the largest invariant set in $\widehat{\Upsilon}$ is the singleton $\{E^*\}$. First, we notice that equality $W'(t)=0$ in (37) occurs if and only if $S(t,a)=S^*$, and

$$\frac{U_1(t)}{U_1^*}\frac{U_2^*}{U_2(t)}=1, \quad \text{and} \quad \frac{U_1^*}{U_1(t)}\frac{U_2(t)}{U_2^*}=1. \tag{39}$$

From conditions (39) it follows that

$$U_2(t)=\frac{U_2^*}{U_1^*}U_1(t). \tag{40}$$

Consequently, using (40) and $S(t,a)=S^*(a)$, we have

$$\begin{aligned}\frac{dU_1(t)}{dt} &= \int_0^\infty \beta(a)U_1(t)S(t,a)da + kU_2(t) - \big(\mu+\delta_1+p\big)U_1(t)\\ &= \int_0^\infty \beta(a)U_1(t)S^*(a)da + k\frac{U_2^*}{U_1^*}U_1(t) - \big(\mu+\delta_1+p\big)U_1(t)\\ &= \frac{U_1(t)}{U_1^*}\left(\int_0^\infty \beta(a)U_1^*S^*(a)da + kU_2^* - \big(\mu+\delta_1+p\big)U_1^*\right)\\ &= 0.\end{aligned} \tag{41}$$

Hence, we must have $U_1(t)=U_1^*$. Thus, we have $U_2(t)=U_2^*$. We conclude that the largest invariant set in $\widehat{\Upsilon}$ is the singleton $\{E^*\}$. Reasoning similarly to the approach in [25] can show that the compact global attractor $\mathcal{A}=\{E^*\}$. Therefore, we conclude that the drug spread equilibrium E^* is globally stable. This completes the proof.

4 Discussion

Recently, some mathematical models (as mentioned in the introduction) have been developed to describe the heroin epidemic. These heroin epidemic models assume that the incidence rate is homogeneous with respect to the age of the susceptible individual. In fact, the individuals with different age may have a different level of susceptibility. In this paper, we present a heroin epidemic model with age-dependent susceptibility, based on the principles of mathematical epidemiology. The model accounts for the incidence rate that depend on the age of the susceptible individuals. 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 reproductive number of heroin use persistence, which gives the number of secondary untreated users that one untreated user will cause in an entirely susceptible population. The reproductive number is the threshold which completely determines the stability of the equilibria. Using a suitable Lyapunov function, we show that the drug-free equilibrium is globally stable if $\mathcal{R}_0 \leq 1$. We also show that if $\mathcal{R}_0 > 1$ the drug-free equilibrium is unstable. In this case there is also a unique drug spread equilibrium which suggests the heroin-use persists in the population. Furthermore, by using a suitable Volterra type Lyapunov function, we establish that the drug spread equilibrium E^* is globally stable for $\mathcal{R}_0 > 1$.

The reproductive number $\mathcal{R}_0$ is an increasing function of $\beta(a)$ (the transmission coefficient function from the susceptible population to heroin user population, i.e., the rate of becoming a drug user at age a), k (the probability of a drug user in treatment relapsing to untreated use), and a decreasing function of p (the rate of drug users who enter treatment). Our mathematical analysis suggest that the spread of the heroin use should be controlled through stringent screening measures of the society to reduce the values of $\beta(a)$ and k, or through campaigns towards the community at all social levels, and towards epidemiologists and treatment providers to increase the values of p. For practical purposes, measures that lead to prevention are better than a cure. Efforts to increase prevention are more effective in controlling the spread of habitual heroin use than efforts to increase the number of individuals accessing treatment. These results provide a view to inform and assist policy-makers in targeting prevention and treatment resources for maximum effectiveness.

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