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Analysis of an age-structured multi-group heroin epidemic model

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Abstract

This paper is concerned with the mathematical analysis of an age-structured multi-group heroin epidemic model, which can be used to describe the spread of heroin habituation and addiction in heterogeneous environment. Under general assumptions on the different level of susceptibility and the relapse to frequent heroin use, we establish sharp criteria for heroin spreading and vanishing. We rigorously investigate the well-posedness of the model, the existence of equilibria, the asymptotic smoothness of solution orbits, and the global stability of equilibria. Specifically, we rigorously show that the drug-free equilibrium is globally asymptotically stable if a threshold value $\mathfrak{R}_0$ is less than one, and the unique drug-endemic equilibrium is globally attractive if $\mathfrak{R}_0$ is greater than one. In the proofs of global stability of equilibria, we construct suitable Lyapunov functions by using a graph-theoretic method.

Keywords: Heroin epidemic, Multi-group model, Age-structured model, Global stability, Lyapunov functions

1. Introduction

The spread of heroin use in population has been called the heroin epidemic, and it has been studied by many authors from the viewpoint of mathematical modelling (see [1–13]). One of the most characteristic features of the heroin epidemic is that the relapse is more likely to occur. That is, heroin users in treatment often return to heroin users without treatment. Thus, most of the heroin epidemic models in the previous study take into account this feature (see [1–13]). The above recent works suggest that modelling and analysis of heroin epidemic models are significant. More precisely, we list some above works by mathematical models quantitatively exploring the heroin epidemic models in the aspects of different differential equations.

In the aspect of ordinary differential equations (ODEs) models, White and Comiskey [1] considered a population divided into three compartments called *susceptible*, *heroin users*, and *heroin users in treatment*. They identified the basic reproduction number R_0 and performed the sensitivity analysis on R_0. In a subsequent work, Mulone and Straughan [2] performed the stability analysis of the model in [1], and gave a confirmed answer that the positive equilibrium of it is stable. For other recent studies on ODEs models for heroin epidemics, see [3–6].

In the aspect of delay differential equations (DDEs) models, Liu and Zhang [7] incorporated time delay to describe the time needed for heroin users in treatment relapsing to heroin users without treatment. They formulated a delayed three compartmental model for heroin epidemics allowing for a relapse distribution, and showed that if $R_0 < 1$, then there exists only the drug-free equilibrium which is globally asymptotically stable; and if $R_0 > 1$ then there is an endemic equilibrium and the disease persists. There was, however, no analytic result on the global stability of equilibrium when $R_0 > 1$ in [7]. In [8], Huang and Liu proved it by constructing a Lyapunov functional. In [9], Fang *et al.* incorporated two types of time delays to describe not only the time stated above but also the time needed for susceptible individuals to become heroin users. Using a suitable Lyapunov function, they established the global threshold dynamics of the model. In [10], Liu and Wang investigated the global threshold dynamics of a multi-group heroin epidemic model with nonlinear incidence rate and distributed delays. In [11], Samanta generalized the model

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in [1] to a nonautonomous model with distributed delay. He obtained two values R_* and R^*, and showed that if $R_* > 1$, then the heroin epidemic will be permanent, whereas if $R^* < 1$, then it will go extinct.

In the aspect of partial differential equations (PDEs) models, a recent work of Fang *et al.* [12] assumed that the susceptibility of individuals varies significantly during their life time. They asserted that the level of susceptibility of individuals may vary due to the development of the immune system and the change of their life style. They constructed and investigated an age-structured heroin epidemic model, in which the incidence rate depends on the age of susceptible individuals. They investigated the global asymptotic properties based on the principles of mathematical epidemiology, and proved that the basic reproduction number completely determines the stability of each equilibrium. In contrast, a model with treat age was studied by Fang *et al.* [13], and some generalized versions of it with nonlinear incidence rates were studied by Yang *et al.* [14] and Djilali *et al.* [15].

Motivated by the work of Fang *et al.* [12, 13], we first consider the following heroin epidemic model with both of the age-dependent susceptibility and treat age.

$$\begin{cases} \left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)S(t,a) = -\beta(a)S(t,a)U_1(t) - \mu S(t,a), & t>0,\ \ a>0, \\ \frac{\mathrm{d}U_1(t)}{\mathrm{d}t} = \int_0^{+\infty}\beta(a)S(t,a)\mathrm{d}aU_1(t) - (\mu+\delta_1+p)U_1(t) + \int_0^{+\infty}\gamma(a)U_2(t,a)\mathrm{d}a, & t>0, \\ \left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)U_2(t,a) = -(\mu+\delta_2+\gamma(a))U_2(t,a), & t>0,\ \ a>0, \\ S(t,0)=\Lambda, \quad U_2(t,0)=pU_1(t), & t>0, \\ S(0,a)=S_0(a), \quad U_1(0)=U_{1,0}, \quad U_2(0,a)=U_{2,0}(a), & a\geq 0. \end{cases} \tag{1.1}$$

Here, t denotes the calendar time and a denotes the class age (time elapsed since the entry in each class). $S(t,a)$, $U_1(t)$ and $U_2(t,a)$ denote the densities of susceptible individuals, heroin users without treatment, and heroin users in treatment, respectively. Λ and μ denote the recruitment rate and the natural death rate, respectively. $\beta(a)$ and $\gamma(a)$ denote the age specific transmission rate, the rate of which heroin users in treatment relapsing to the untreated class, respectively. p denotes the rate of which drug users untreated class entering into heroin users in treatment class, δ_1 and δ_2 denote the removal rate from the heroin users untreated and treated class, respectively, of which including the rates of heroin-related deaths and recovery from the drug-life with permanent immunity. In this study, to make things not too complicated, we restrict our attention on the simplest constant recruitment rate Λ, which is thought to be standard for heroin epidemic models (see [1–10, 12, 13]). We remark that the case of variable recruitment rate $\Lambda(t)$ (see, e.g., [11]) is an important future subject, in which the system becomes nonautonomous.

In this study, we further incorporate the multi-group structure into model (1.1), which enables us to consider the heterogeneity (sex, position, etc.) of each individual. During the past decades, multi-group epidemic models have attracted much attention (see [10, 16–20] and the references therein). Let us divide the heterogeneous population into $n \in \mathbb{N}$ homogeneous groups, and let $\mathcal{N} := \{1, 2, \cdots, n\}$. Each group is further divided into three disjoint classes as in (1.1): susceptible class S_i, heroin users without treatment U_{1i} and heroin users in treatment U_{2i} for each group $i \in \mathcal{N}$. Then, the multi-group heroin epidemic model is formulated as the following nonlinear coupled system of partial and ordinary differential equations, which is a generalization of the model (1.1).

$$\begin{cases} \left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)S_i(t,a) = -\sum_{j=1}^{n}\beta_{ij}(a)S_i(t,a)U_{1j}(t) - \mu_i S_i(t,a), & t>0,\ \ a>0,\ \ i\in\mathcal{N}, \\ \frac{\mathrm{d}U_{1i}(t)}{\mathrm{d}t} = \sum_{j=1}^{n}\int_0^{+\infty}\beta_{ij}(a)S_i(t,a)\mathrm{d}aU_{1j}(t) - (\mu_i+\delta_{1i}+p_i)\,U_{1i}(t) + \int_0^{+\infty}\gamma_i(a)U_{2i}(t,a)\mathrm{d}a, & t>0,\ \ i\in\mathcal{N}, \\ \left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)U_{2i}(t,a) = -\left(\mu_i+\delta_{2i}+\gamma_i(a)\right)U_{2i}(t,a), & t>0,\ \ a>0,\ \ i\in\mathcal{N}, \\ S_i(t,0)=\Lambda_i, \ \ U_{2i}(t,0)=p_iU_{1i}(t), & t>0,\ \ i\in\mathcal{N}, \\ S_i(0,a)=S_{i,0}(a), \ \ U_{1i}(0)=U_{1i,0}, \ \ U_{2i}(0,a)=U_{2i,0}(a), & a\geq 0,\ \ i\in\mathcal{N}. \end{cases} \tag{1.2}$$

Biological meaning of each parameter in (1.2) is similar to that in (1.1) although it depends on the group (see Table B.1). We make the following assumption on the parameters.

Assumption 1.1. *(i)* $\Lambda_i > 0$, $\mu_i > 0$, $p_i > 0$, $\delta_{1i} > 0$ *and* $\delta_{2i} > 0$ *for all* $i \in \mathcal{N}$*;*

(ii) $\gamma_i(\cdot) \in L^\infty_+(0, +\infty)$ *with essential upper bound* $\gamma_i^+ \in (0, +\infty)$ *for all* $i \in \mathcal{N}$. $\gamma_i(a) > 0$ *for all* $a \geq 0$ *and* $i \in \mathcal{N}$*;*

(iii) $\beta_{ij}(\cdot) \in L^\infty_+(0, +\infty) \cap L^1_+(0, +\infty)$ *with essential upper bound* $\beta_{ij}^+ \in (0, +\infty)$ *for all* $i, j \in \mathcal{N}$*. The n-square matrix* $\left(\int_0^{+\infty} \beta_{ij}(a)\mathrm{d}a\right)_{i,j\in\mathcal{N}}$ *is irreducible ([21]). There exists a* $\tilde{\beta}(\cdot) \in L^1_+(0, +\infty)$ *such that* $\beta_{ij}(a) \leq \tilde{\beta}(a)$ *for all* $a \geq 0$ *and* $i, j \in \mathcal{N}$*.*

The purpose of this study is to clarify the global asymptotic behavior of system (1.2). We obtain a threshold value $\mathfrak{R}_0$ in connection with the existence of a positive drug-endemic equilibrium of (1.2), and show that it determines the global asymptotic stability (or attractivity) of each equilibrium: if $\mathfrak{R}_0 < 1$, then the drug-free equilibrium is globally asymptotically stable, whereas if $\mathfrak{R}_0 > 1$, then the drug-endemic equilibrium uniquely exists and it is globally attractive. That is, nontrivial bifurcations (backward bifurcation, Hopf bifurcation, etc.) do not occur at $\mathfrak{R}_0 = 1$ (see [3, 6] for studies on such bifurcations in heroin epidemic models), and social efforts for reducing $\mathfrak{R}_0$ less than 1 have significance in the eradication of the heroin epidemic.

The rest of paper is organized as follows. In Section 2, we prove the existence and uniqueness of each equilibrium. It is shown that the drug-free equilibrium always exists, whereas the drug-endemic equilibrium uniquely exists if $\mathfrak{R}_0 > 1$ (see Theorem 2.1 and 2.2). In Section 3, we prove that the solution of the model exists globally by following the procedure of the integrated semigroup formulation of system (1.2). Section 4 is devoted to show the asymptotic smoothness of the semiflow generated by system (1.2). In Section 5, we prove that drug-free equilibrium is globally asymptotically stable for $\mathfrak{R}_0 < 1$. In the proof, we first prove that the drug-free equilibrium is locally asymptotically stable by analyzing characteristic equation, and then prove that it is globally attractive by following the procedure of constructing a suitable Lyapunov function and using an invariance principle. In Section 6, the persistence of the heroin users without treatment for $\mathfrak{R}_0 > 1$ is proved, which is important for the construction of a Lyapunov function in Section 7. In Section 7, the global attractivity of the drug-endemic equilibrium of system (1.2) for $\mathfrak{R}_0 > 1$ is proved. We perform numerical simulation to illustrate our theoretical results in Section 8. We conclude the paper by Section 9, where some detailed conclusions and discussions are presented. For a special case ($n = 2$), we suggest whether prevention or cure (treatment) are more suitable for male and female heroin user under reasonable circumstance.

2. Drug-free and drug-endemic equilibria

Let $X := L^1(0, +\infty; \mathbb{R}^n) \times \mathbb{R}^n \times L^1(0, +\infty; \mathbb{R}^n)$ and $X_+ := L^1_+(0, +\infty; \mathbb{R}^n) \times \mathbb{R}^n_+ \times L^1_+(0, +\infty; \mathbb{R}^n)$. Equilibria of system (1.2) can be obtained by solving the following equations.

$$\begin{cases} \dfrac{\mathrm{d}\tilde{S}_i(a)}{\mathrm{d}a} = -\displaystyle\sum_{j=1}^n \beta_{ij}(a)\tilde{S}_i(a)\tilde{U}_{1j} - \mu_i\tilde{S}_i(a), & a > 0, \ \ i \in \mathcal{N}, \\ 0 = \displaystyle\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)\tilde{S}_i(a)\mathrm{d}a\tilde{U}_{1j} - (\mu_i + \delta_{1i} + p_i)\,\tilde{U}_{1i} + \int_0^{+\infty} \gamma_i(a)\tilde{U}_{2i}(a)\mathrm{d}a, & i \in \mathcal{N}, \\ \dfrac{\mathrm{d}\tilde{U}_{2i}(a)}{\mathrm{d}a} = -(\mu_i + \delta_{2i} + \gamma_i(a))\,\tilde{U}_{2i}(a), & a > 0, \ \ i \in \mathcal{N}, \\ \tilde{S}_i(0) = \Lambda_i, \ \ \tilde{U}_{2i}(0) = p_i\tilde{U}_{1i}, & i \in \mathcal{N}. \end{cases} \tag{2.1}$$

When $\tilde{U}_{1i} = 0$ for all $i \in \mathcal{N}$, the following drug-free equilibrium can be obtained:

$$E^0 : \left(\tilde{S}_1(\cdot), \cdots, \tilde{S}_n(\cdot), \tilde{U}_{11}, \cdots, \tilde{U}_{1n}, \tilde{U}_{21}(\cdot), \cdots, \tilde{U}_{2n}(\cdot)\right)^{\mathrm{T}} = \left(S_1^0(\cdot), \cdots, S_n^0(\cdot), 0_{\mathbb{R}^n}, 0_{L^1(0,+\infty;\mathbb{R}^n)}\right)^{\mathrm{T}} \in X_+,$$

where $S_i^0(a) := \Lambda_i \mathrm{e}^{-\mu_i a}$ for all $i \in \mathcal{N}$, and T denotes the transpose operation. It is easy to see that E^0 always exists.

When $\tilde{U}_{1i} > 0$ for some or all $i \in \mathcal{N}$, the drug-endemic equilibrium can be obtained. We denote it by

$$E^* : \left(\tilde{S}_1(\cdot), \cdots, \tilde{S}_n(\cdot), \tilde{U}_{11}, \cdots, \tilde{U}_{1n}, \tilde{U}_{21}(\cdot), \cdots, \tilde{U}_{2n}(\cdot)\right)^{\mathrm{T}} = \left(S_1^*(\cdot), \cdots, S_n^*(\cdot), U_{11}^*, \cdots, U_{1n}^*, U_{21}^*(\cdot), \cdots, U_{2n}^*(\cdot)\right)^{\mathrm{T}} \in X_+.$$

Now, we investigate the existence and uniqueness of E^*. From (2.1), we see that the components of E^* satisfy the following equations.

$$\begin{cases} \dfrac{\mathrm{d}S_i^*(a)}{\mathrm{d}a} = -\left(\displaystyle\sum_{j=1}^n \beta_{ij}(a)U_{1j}^* + \mu_i\right) S_i^*(a), & a > 0, \ i \in \mathcal{N}, \\ (\mu_i + \delta_{1i} + p_i)U_{1i}^* = \displaystyle\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i^*(a)\mathrm{d}a U_{1j}^* + \int_0^{+\infty} \gamma_i(a)U_{2i}^*(a)\mathrm{d}a, & i \in \mathcal{N}, \\ \dfrac{\mathrm{d}U_{2i}^*(a)}{\mathrm{d}a} = -\left(\mu_i + \delta_{2i} + \gamma_i(a)\right) U_{2i}^*(a), & a > 0, \ i \in \mathcal{N}, \\ S_i^*(0) = \Lambda_i, \ \ U_{2i}^*(0) = p_i U_{1i}^*, & i \in \mathcal{N}. \end{cases} \tag{2.2}$$

Integrating the first and third equations in (2.2), we have

$$\begin{cases} S_i^*(a) = \Lambda_i \mathrm{e}^{-\sum_{j=1}^n U_{1j}^* \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma - \mu_i a} = S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n U_{1j}^* \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}, & a \geq 0, \ i \in \mathcal{N}, \\ U_{2i}^*(a) = p_i U_{1i}^* \mathrm{e}^{-\int_0^a (\mu_i + \delta_{2i} + \gamma_i(\sigma))\mathrm{d}\sigma}, & a \geq 0, \ i \in \mathcal{N}. \end{cases} \tag{2.3}$$

Substituting them into the second equation in (2.2), we have

$$(\mu_i + \delta_{1i} + p_i)U_{1i}^* = \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n U_{1j}^* \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}\mathrm{d}a U_{1j}^* + p_i U_{1i}^* \theta_i, \quad i \in \mathcal{N},$$

where $\theta_i := \int_0^{+\infty} \gamma_i(a)\varrho_i(a)\mathrm{d}a$, $\varrho_i(a) := \mathrm{e}^{-\int_0^a \alpha_i(\sigma)\mathrm{d}\sigma}$ and $\alpha_i(a) := \mu_i + \delta_{2i} + \gamma_i(a)$ for all $a \geq 0$ and $i \in \mathcal{N}$. Hence,

$$U_{1i}^* = \sum_{j=1}^n \frac{\int_0^{+\infty} \beta_{ij}(a)S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n U_{1j}^* \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} U_{1j}^*, \quad i \in \mathcal{N}. \tag{2.4}$$

Note that $1 - \theta_i > 0$ for all $i \in \mathcal{N}$. In fact, $0 \leq \theta_i = \int_0^{+\infty} \gamma_i(a)\varrho_i(a)\mathrm{d}a < \int_0^{+\infty} \gamma_i(a)\mathrm{e}^{-\int_0^a \gamma_i(\sigma)\mathrm{d}\sigma}\mathrm{d}a \leq 1$ for all $i \in \mathcal{N}$. To investigate the existence of the drug-endemic equilibrium, we will employ the fixed-point problem of the following nonlinear operator Ψ on $\mathbb{R}_+^n$.

$$\Psi(\varphi) := \left(\sum_{j=1}^n \frac{\int_0^{+\infty} \beta_{ij}(a)S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n \varphi_j \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i}\varphi_j\right)_{i \in \mathcal{N}}, \quad \varphi = (\varphi_1, \varphi_2, \cdots, \varphi_n)^{\mathrm{T}} \in \mathbb{R}_+^n. \tag{2.5}$$

If the operator Ψ has the positive fixed point $\varphi^* \in \mathbb{R}_+^n \setminus \{0_{\mathbb{R}^n}\}$ such that $\Psi(\varphi^*) = \varphi^*$, then it is no other than the positive U_{1i}^*, $i \in \mathcal{N}$ satisfying (2.4) and hence, from (2.3), the existence of the drug-endemic equilibrium E^* follows. It is easy to check that the Fréchet derivative of the operator Ψ at the origin $0_{\mathbb{R}^n}$ is given by the following matrix:

$$\Psi'[0_{\mathbb{R}^n}] = \left(\frac{\int_0^{+\infty} \beta_{ij}(a)S_i^0(a)\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i}\right)_{i,j \in \mathcal{N}} =: M^0. \tag{2.6}$$

In what follows, we define $\mathfrak{R}_0 := r(M^0)$, where $r(\cdot)$ denotes the spectral radius of a matrix M^0. Since matrix M^0 is nonnegative and irreducible under Assumption 1.1, it follows from the Perron-Frobenius theorem (see [21]) that $\mathfrak{R}_0 = r(M^0)$ is a positive eigenvalue of M^0, associated with a strictly positive eigenvector. By constructing a monotone nondecreasing sequence, we can prove the following theorem on the existence of the drug-endemic equilibrium E^*:

Theorem 2.1. *If* $\mathfrak{R}_0 > 1$*, then system* (1.2) *has at least one drug-endemic equilibrium* E^*.

Proof. For $\varphi = (\varphi_1, \varphi_2, \cdots, \varphi_n)^{\mathrm{T}} \in \mathbb{R}_+^n$, it follows from (2.5) that

$$\Psi(\varphi) = \left(\frac{\int_0^{+\infty} \sum_{j=1}^n \varphi_j \beta_{ij}(a) \mathrm{e}^{-\sum_{j=1}^n \varphi_j \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma} S_i^0(a)\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} \right)_{i\in\mathcal{N}}$$
$$= \left(\frac{\left[-\mathrm{e}^{-\sum_{j=1}^n \varphi_j \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma} S_i^0(a) \right]_0^{+\infty} - \mu_i \int_0^{+\infty} \mathrm{e}^{-\sum_{j=1}^n \varphi_j \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma} S_i^0(a)\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} \right)_{i\in\mathcal{N}} = \left(\frac{\Lambda_i - \mu_i \int_0^{+\infty} \mathrm{e}^{-\sum_{j=1}^n \varphi_j \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma} S_i^0(a)\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} \right)_{i\in\mathcal{N}}. \tag{2.7}$$

Hence, Ψ is monotone nondecreasing with respect to φ (that is, $\Psi(\varphi) \geq \Psi(\psi)$ if $\varphi \geq \psi$ in $\mathbb{R}_+^n$) and uniformly bounded with the upper bound: $\|\Psi(\varphi)\| \leq \sum_{i=1}^n \Lambda_i / (\mu_i + \delta_{1i} + (1-\theta_i)p_i)$, where $\|\cdot\|$ denotes the norm in $\mathbb{R}^n$ defined by $\|\varphi\| := \sum_{i=1}^n |\varphi_i|$, $\varphi = (\varphi_1, \varphi_2, \cdots, \varphi_n)^{\mathrm{T}} \in \mathbb{R}^n$. As stated above, $\mathfrak{R}_0 = r(M^0) > 1$ is a positive eigenvalue of M^0, associated with a strictly positive eigenvector $v = (v_1, v_2, \cdots, v_n)^{\mathrm{T}}$. Let us define $w = (w_1, w_2, \cdots, w_n)^{\mathrm{T}}$ by $w := \ln r(M^0) v / (\|v\| \left\|\tilde{\beta}\right\|_{L^1})$. Then, we have

$$\Psi(w) = \left(\frac{\int_0^{+\infty} \sum_{j=1}^n w_j \beta_{ij}(a) \mathrm{e}^{-\ln r(M^0) \frac{\sum_{j=1}^n v_j \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}{\|v\| \left\|\tilde{\beta}\right\|_{L^1}}} S_i^0(a)\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} \right)_{i\in\mathcal{N}} \geq \left(\frac{\int_0^{+\infty} \sum_{j=1}^n w_j \beta_{ij}(a) \mathrm{e}^{-\ln r(M^0)} S_i^0(a)\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} \right)_{i\in\mathcal{N}}$$
$$= \frac{1}{r(M^0)} \left(\sum_{j=1}^n \frac{\int_0^{+\infty} \beta_{ij}(a) S_i^0(a)\mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} w_j \right)_{i\in\mathcal{N}} = \frac{1}{r(M^0)} M^0 w = \frac{1}{r(M^0)} \frac{\ln r(M^0)}{\|v\| \left\|\tilde{\beta}\right\|_{L^1}} M^0 v = \frac{1}{r(M^0)} \frac{\ln r(M^0)}{\|v\| \left\|\tilde{\beta}\right\|_{L^1}} r(M^0) v = \frac{\ln r(M^0)}{\|v\| \left\|\tilde{\beta}\right\|_{L^1}} v = w.$$

Hence, from the monotonicity of Ψ, we can construct the monotone nondecreasing sequence $\{\Psi^m(w)\}_{m=0}^{+\infty}$ such that $\Psi^{m+1}(w) \geq \Psi^m(w)$ for all $m = 0, 1, 2, \cdots$. Since Ψ is uniformly bounded, the sequence has a limit $w^\infty := \lim_{m\to+\infty} \Psi^m(w)$ such that $w^\infty = \Psi(w^\infty)$. Thus, w^∞ is no other than the desired nontrivial fixed-point of Ψ and the system (1.2) has at least one drug-endemic equilibrium E^*. □

On the uniqueness of the drug-endemic equilibrium E^*, we prove the following theorem.

Theorem 2.2. *System* (1.2) *has at most one drug-endemic equilibrium* E^*.

Proof. Let us consider another endemic equilibrium of (1.2) in the following notation: $\hat{E} : \left(\hat{S}_1(\cdot), \cdots, \hat{S}_n(\cdot), \hat{U}_{11}, \cdots, \hat{U}_{1n}, \hat{U}_{21}(\cdot), \cdots, \hat{U}_{2n}(\cdot)\right)^{\mathrm{T}} \in X_+$. Suppose that $\mathbf{U}_1^* \neq \hat{\mathbf{U}}_1$, where $\mathbf{U}_1^* := \left(U_{11}^*, \cdots, U_{1n}^*\right)^{\mathrm{T}}$ and $\hat{\mathbf{U}}_1 := \left(\hat{U}_{11}, \cdots, \hat{U}_{1n}\right)^{\mathrm{T}}$. Note that under Assumption 1.1, it follows from (2.4) that $U_{1i}^* > 0$ and $\hat{U}_{1i} > 0$ for all $i \in \mathcal{N}$. There exist a positive constant $\eta > 0$ and a nonempty subset $\tilde{\mathcal{N}} \subseteq \mathcal{N}$ such that $U_{1i}^* = \eta \hat{U}_{1i}$ for all $i \in \tilde{\mathcal{N}}$, and $U_{1i}^* > \eta \hat{U}_{1i}$ for all $i \in \mathcal{N} \setminus \tilde{\mathcal{N}}$. From the monotonicity of operator Ψ (see (2.7)), we have

$$\mathbf{U}_1^* = \Psi(\mathbf{U}_1^*) \geq \Psi\left(\eta \hat{\mathbf{U}}_1\right). \tag{2.8}$$

Suppose that $\eta \in (0, 1)$. From (2.5), we have

$$\Psi\left(\eta \hat{\mathbf{U}}_1\right) = \left(\sum_{j=1}^n \frac{\int_0^{+\infty} \beta_{ij}(a) S_i^0(a) \mathrm{e}^{-\sum_{j=1}^n \eta \hat{U}_{1j} \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma} \mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} \eta \hat{U}_{1j} \right)_{i\in\mathcal{N}} \gg \eta \left(\sum_{j=1}^n \frac{\int_0^{+\infty} \beta_{ij}(a) S_i^0(a) \mathrm{e}^{-\sum_{j=1}^n \hat{U}_{1j} \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma} \mathrm{d}a}{\mu_i + \delta_{1i} + (1-\theta_i)p_i} \hat{U}_{1j} \right)_{i\in\mathcal{N}}$$
$$= \eta \Psi\left(\hat{\mathbf{U}}_1\right) = \eta \hat{\mathbf{U}}_1, \tag{2.9}$$

where $\gg$ implies that the strict inequality $>$ holds for each element of vectors. From (2.8) and (2.9), we have $U_{1i}^* > \eta \hat{U}_{1i}$ for any $i \in \tilde{\mathcal{N}}$, which is a contradiction. Hence, $\eta \geq 1$, and thus, $\mathbf{U}_1^* \geq \eta \hat{\mathbf{U}}_1 \geq \hat{\mathbf{U}}_1$. Exchanging the roles of $\mathbf{U}_1^*$ and $\hat{\mathbf{U}}_1$, we can prove in a similar way that $\hat{\mathbf{U}}_1 \geq \mathbf{U}_1^*$. Consequently, we have $\mathbf{U}_1^* = \hat{\mathbf{U}}_1$. From (2.3), we see that $S_i^*(\cdot) = \hat{S}_i(\cdot)$ and $U_{2i}^*(\cdot) = \hat{U}_{2i}(\cdot)$ for all $i \in \mathcal{N}$. This completes the proof. □

3. Integrated semigroup formulation

We now use the approach introduced by Thieme [22] to reformulate the system (1.2) into an abstract Cauchy problem. Let $\mathbb{X} := \mathbb{R}^n \times L^1(0,+\infty;\mathbb{R}^n) \times \mathbb{R}^n \times \mathbb{R}^n \times L^1(0,+\infty;\mathbb{R}^n)$ and $\mathbb{X}_0 := \{0_{\mathbb{R}^n}\} \times L^1(0,+\infty;\mathbb{R}^n) \times \mathbb{R}^n \times \{0_{\mathbb{R}^n}\} \times L^1(0,+\infty;\mathbb{R}^n) \subset \mathbb{X}$, and let $\mathbb{X}_+$ and $\mathbb{X}_{0,+}$ be their respective positive cones. Let us define the norm $\|\cdot\|_{\mathbb{X}}$ on $\mathbb{X}$ as follows.

$$\left\|(\phi_1,\psi_1,\varphi,\phi_2,\psi_2)^{\mathrm{T}}\right\|_{\mathbb{X}} := \sum_{i=1}^{n}\left|\phi_{1,i}\right| + \sum_{i=1}^{n}\int_0^{+\infty}|\psi_{1,i}(a)|\mathrm{d}a + \sum_{i=1}^{n}|\varphi_i| + \sum_{i=1}^{n}|\phi_{2,i}| + \sum_{i=1}^{n}\int_0^{+\infty}|\psi_{2,i}(a)|\mathrm{d}a,$$

where $\phi_1 := (\phi_{1,1},\phi_{1,2},\cdots,\phi_{1,n})^{\mathrm{T}} \in \mathbb{R}^n$, $\psi_1 := (\psi_{1,1}(\cdot),\psi_{1,2}(\cdot),\cdots,\psi_{1,n}(\cdot))^{\mathrm{T}} \in L^1(0,+\infty;\mathbb{R}^n)$, $\varphi := (\varphi_1,\varphi_2,\cdots,\varphi_n)^{\mathrm{T}} \in \mathbb{R}^n$, $\phi_2 := (\phi_{2,1},\phi_{2,2},\cdots,\phi_{2,n})^{\mathrm{T}} \in \mathbb{R}^n$ and $\psi_2 := (\psi_{2,1}(\cdot),\psi_{2,2}(\cdot),\cdots,\psi_{2,n}(\cdot))^{\mathrm{T}} \in L^1(0,+\infty;\mathbb{R}^n)$. To reformulate the system (1.2) into the abstract Cauchy problem, we define the following two operators A and F on $\mathbb{X}_0$.

$$A\begin{pmatrix}0_{\mathbb{R}^n}\\ \psi_1\\ \varphi\\ 0_{\mathbb{R}^n}\\ \psi_2\end{pmatrix} := \begin{pmatrix}-\psi_1(0)\\ -\dfrac{\mathrm{d}\psi_1(a)}{\mathrm{d}a}-\mathbf{Q}_1\psi_1(a)\\ -\mathbf{Q}_2\varphi\\ -\psi_2(0)\\ -\dfrac{\mathrm{d}\psi_2(a)}{\mathrm{d}a}-\mathbf{Q}_3(a)\psi_2(a)\end{pmatrix},\quad \begin{pmatrix}0_{\mathbb{R}^n}\\ \psi_1\\ \varphi\\ 0_{\mathbb{R}^n}\\ \psi_2\end{pmatrix} \in D(A) := \{0_{\mathbb{R}^n}\}\times W^{1,1}(0,+\infty;\mathbb{R}^n)\times\mathbb{R}^n\times\{0_{\mathbb{R}^n}\}\times W^{1,1}(0,+\infty;\mathbb{R}^n),$$

$$F\begin{pmatrix}0_{\mathbb{R}^n}\\ \psi_1\\ \varphi\\ 0_{\mathbb{R}^n}\\ \psi_2\end{pmatrix} := \begin{pmatrix}\mathbf{\Lambda}\\ -\mathbf{B}(\varphi)(a)\psi_1(a)\\ \int_0^{+\infty}\mathbf{B}(\varphi)(a)\psi_1(a)\mathrm{d}a+\int_0^{+\infty}\mathbf{\Gamma}(a)\psi_2(a)\mathrm{d}a\\ \mathbf{P}\varphi\\ 0_{L^1(0,+\infty;\mathbb{R}^n)}\end{pmatrix},\quad \begin{pmatrix}0_{\mathbb{R}^n}\\ \psi_1\\ \varphi\\ 0_{\mathbb{R}^n}\\ \psi_2\end{pmatrix} \in \mathbb{X}_0, \tag{3.1}$$

where $W^{1,1}(0,+\infty;\mathbb{R}^n)$ denotes the Sobolev space, and $\mathbf{Q}_1 := \mathrm{diag}_{i\in\mathcal{N}}(\mu_i)$, $\mathbf{Q}_2 := \mathrm{diag}_{i\in\mathcal{N}}(\mu_i+\delta_{1i}+p_i)$, $\mathbf{Q}_3(a) := \mathrm{diag}_{i\in\mathcal{N}}(\mu_i+\delta_{2i}+\gamma_i(a))$, $\mathbf{\Lambda} := \mathrm{diag}_{i\in\mathcal{N}}(\Lambda_i)$, $\mathbf{B}(\varphi)(a) := \mathrm{diag}_{i\in\mathcal{N}}\left(\sum_{j=1}^{n}\beta_{ij}(a)\varphi_j\right)$, $\mathbf{\Gamma}(a) := \mathrm{diag}_{i\in\mathcal{N}}(\gamma_i(a))$ and $\mathbf{P} := \mathrm{diag}_{i\in\mathcal{N}}(p_i)$. Note that $D(A)\subset\mathbb{X}_0$ and $\overline{D(A)}=\mathbb{X}_0$. Let

$$\mathbf{x}(t) := (0_{\mathbb{R}^n},\mathbf{S}(t,\cdot),\mathbf{U}_1(t),0_{\mathbb{R}^n},\mathbf{U}_2(t,\cdot))^{\mathrm{T}} \quad\text{and}\quad \mathbf{x}_0 := \mathbf{x}(0) = \left(0_{\mathbb{R}^n},\mathbf{S}_0(\cdot),\mathbf{U}_{1,0},0_{\mathbb{R}^n},\mathbf{U}_{2,0}(\cdot)\right)^{\mathrm{T}},$$

where $\mathbf{S}(t,\cdot) := (S_1(t,\cdot),\cdots,S_n(t,\cdot))^{\mathrm{T}}$, $\mathbf{U}_1(t) := (U_{11}(t),\cdots,U_{1n}(t))^{\mathrm{T}}$, $\mathbf{U}_2(t,\cdot) := (U_{21}(t,\cdot),\cdots,U_{2n}(t,\cdot))^{\mathrm{T}}$, $\mathbf{S}_0(\cdot) := (S_{1,0}(\cdot),\cdots,S_{n,0}(\cdot))^{\mathrm{T}}$, $\mathbf{U}_{1,0} := (U_{11,0},\cdots,U_{1n,0})^{\mathrm{T}}$ and $\mathbf{U}_{2,0}(\cdot) := (U_{21,0}(\cdot),\cdots,U_{2n}(\cdot))^{\mathrm{T}}$. Under this setting, we rewrite the problem (1.2) into the following abstract Cauchy problem:

$$\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = A\mathbf{x}(t)+F(\mathbf{x}(t)),\quad t>0,\quad \mathbf{x}(0)=\mathbf{x}_0\in\overline{D(A)}\cap\mathbb{X}_{0,+}. \tag{3.2}$$

To prove the existence and uniqueness of the global classical solution to (3.2), we use the results in [23]. To this end, we first prove the following lemma.

Lemma 3.1. (i) *There exist real constants $M\geq 1$ and $\omega\in\mathbb{R}$ such that $(\omega,+\infty)\subset\rho(A)$, and*

$$\left\|(\lambda I-A)^{-n}\right\| \leq \frac{M}{(\lambda-\omega)^n} \quad\text{for all } n\in\mathbb{N} \text{ and } \lambda>\omega, \tag{3.3}$$

where $\rho(A)$ denotes the resolvent set of A, and I denotes the identity operator. Furthermore, for all $\lambda>\omega$, $(\lambda I-A)^{-1}(\mathbb{X}_+)\subset\mathbb{X}_+$.

(ii) *For all $C>0$, there exists $K(C)>0$ such that*

$$\|F(\varrho)-F(\hat{\varrho})\|_{\mathbb{X}} \leq K(C)\|\varrho-\hat{\varrho}\|_{\mathbb{X}} \quad\text{for all } \varrho := (0_{\mathbb{R}^n},\psi_1,\varphi,0_{\mathbb{R}^n},\psi_2)^{\mathrm{T}} \in \mathbb{X}_0\cap\bar{B}_C(0)$$
$$\text{and } \hat{\varrho} := \left(0_{\mathbb{R}^n},\hat{\psi}_1,\hat{\varphi},0_{\mathbb{R}^n},\hat{\psi}_2\right)^{\mathrm{T}} \in \mathbb{X}_0\cap\bar{B}_C(0), \tag{3.4}$$

where $\bar{B}_C(0) := \{\varrho\in\mathbb{X}_0 : \|\varrho\|_{\mathbb{X}}\leq C\}$.

Proof. (i) Let $\mu^- := \min_{i\in\mathcal{N}}\{\mu_i\}$ and $\lambda > -\mu^-$. For any $(\phi_1,\psi_1,\varphi,\phi_2,\psi_2)^{\mathrm{T}} \in \mathbb{X}$, we easily see that

$$(\lambda I - A)^{-1}\begin{pmatrix}\phi_1\\ \psi_1\\ \varphi\\ \phi_2\\ \psi_2\end{pmatrix} = \begin{pmatrix}0_{\mathbb{R}^n}\\ \hat\psi_1\\ \hat\varphi\\ 0_{\mathbb{R}^n}\\ \hat\psi_2\end{pmatrix} \quad \text{implies} \quad \begin{pmatrix}\phi_1\\ \psi_1\\ \varphi\\ \phi_2\\ \psi_2\end{pmatrix} = \begin{pmatrix}\hat\psi_1(0)\\ \dfrac{\mathrm{d}}{\mathrm{d}a}\hat\psi_1(a) + (\lambda I + \mathbf{Q}_1)\,\psi_1(a)\\ (\lambda I + \mathbf{Q}_2)\,\hat\varphi\\ \hat\psi_2(0)\\ \dfrac{\mathrm{d}}{\mathrm{d}a}\hat\psi_2(a) + (\lambda I + \mathbf{Q}_3)\,\psi_2(a)\end{pmatrix},$$

and hence,

$$\hat\psi_{1,i}(a) = \phi_{1,i}\mathrm{e}^{-(\lambda+\mu_i)a} + \int_0^a \psi_{1,i}(\sigma)\mathrm{e}^{-(\lambda+\mu_i)(a-\sigma)}\mathrm{d}\sigma, \quad \hat\varphi_i = \frac{\varphi_i}{\lambda+\mu_i+\delta_{1i}+p_i},$$
$$\hat\psi_{2,i}(a) = \phi_{2,i}\mathrm{e}^{-\int_0^a(\lambda+\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma} + \int_0^a \psi_{2,i}(\sigma)\mathrm{e}^{-\int_\sigma^a(\lambda+\mu_i+\delta_{2i}+\gamma_i(\rho))\mathrm{d}\rho}\mathrm{d}\sigma, \quad i \in \mathcal{N}.$$

Hence, the latter part of (i) follows. Now, we have the following norm estimate.

$$\left\|(\lambda I - A)^{-1}\begin{pmatrix}\phi_1\\ \psi_1\\ \varphi\\ \phi_2\\ \psi_2\end{pmatrix}\right\|_{\mathbb{X}} = \sum_{i=1}^n 0 + \sum_{i=1}^n\int_0^{+\infty}\left|\hat\psi_{1,i}(a)\right|\mathrm{d}a + \sum_{i=1}^n|\hat\varphi_i| + \sum_{i=1}^n 0 + \sum_{i=1}^n\int_0^{+\infty}\left|\hat\psi_{2,i}(a)\right|\mathrm{d}a$$
$$\le \sum_{i=1}^n\int_0^{+\infty}\left|\phi_{1,i}\right|\mathrm{e}^{-(\lambda+\mu_i)a}\mathrm{d}a + \sum_{i=1}^n\int_0^{+\infty}\int_0^a\left|\psi_{1,i}(\sigma)\right|\mathrm{e}^{-(\lambda+\mu_i)(a-\sigma)}\mathrm{d}\sigma\mathrm{d}a + \sum_{i=1}^n\frac{|\varphi_i|}{|\lambda+\mu_i+\delta_{1i}+p_i|}$$
$$+ \sum_{i=1}^n\int_0^{+\infty}\left|\phi_{2,i}\right|\mathrm{e}^{-\int_0^a(\lambda+\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}\mathrm{d}a + \sum_{i=1}^n\int_0^{+\infty}\int_0^a\left|\psi_{2,i}(\sigma)\right|\mathrm{e}^{-\int_\sigma^a(\lambda+\mu_i+\delta_{2i}+\gamma_i(\rho))\mathrm{d}\rho}\mathrm{d}\sigma\mathrm{d}a$$
$$\le \sum_{i=1}^n\frac{\left|\phi_{1,i}\right|}{\lambda+\mu^-} + \sum_{i=1}^n\frac{\left\|\psi_{1,i}\right\|_{L^1}}{\lambda+\mu^-} + \sum_{i=1}^n\frac{|\varphi_i|}{\lambda+\mu^-} + \sum_{i=1}^n\frac{\left|\phi_{2,i}\right|}{\lambda+\mu^-} + \sum_{i=1}^n\frac{\left\|\psi_{2,i}\right\|_{L^1}}{\lambda+\mu^-} = \frac{1}{\lambda+\mu^-}\left\|\begin{pmatrix}\phi_1\\ \psi_1\\ \varphi\\ \phi_2\\ \psi_2\end{pmatrix}\right\|_{\mathbb{X}}.$$

Hence, (3.3) holds for $M = 1$ and $\omega = -\mu^-$.

(ii) For any $\varrho, \hat\varrho \in \mathbb{X}_0 \cap \bar B_C(0)$, we have

$$\|F(\varrho) - F(\hat\varrho)\|_{\mathbb{X}} = \left\|\begin{pmatrix}0_{\mathbb{R}^n}\\ -\mathbf{B}(\varphi)(a)\psi_1(a) + \mathbf{B}(\hat\varphi)(a)\hat\psi_1(a)\\ \int_0^{+\infty}\mathbf{B}(\varphi)(a)\psi_1(a)\mathrm{d}a + \int_0^{+\infty}\mathbf{\Gamma}(a)\psi_2(a)\mathrm{d}a - \int_0^{+\infty}\mathbf{B}(\hat\varphi)(a)\hat\psi_1(a)\mathrm{d}a - \int_0^{+\infty}\mathbf{\Gamma}(a)\hat\psi_2(a)\mathrm{d}a\\ \mathbf{P}\varphi - \mathbf{P}\hat\varphi\\ 0_{L^1(0,+\infty;\mathbb{R}^n)}\end{pmatrix}\right\|_{\mathbb{X}}$$
$$\le 2\sum_{i=1}^n\int_0^{+\infty}\left|\sum_{j=1}^n\beta_{ij}(a)\varphi_j\psi_{1,i}(a) - \sum_{j=1}^n\beta_{ij}(a)\hat\varphi_j\hat\psi_{1,i}(a)\right|\mathrm{d}a + \sum_{i=1}^n\int_0^{+\infty}\left|\gamma_i(a)\psi_{2,i}(a) - \gamma_i(a)\hat\psi_{2,i}(a)\right|\mathrm{d}a + \sum_{i=1}^n|p_i\varphi_i - p_i\hat\varphi_i|$$
$$\le 2\sum_{i=1}^n\int_0^{+\infty}\left|\sum_{j=1}^n\beta_{ij}(a)\varphi_j\psi_{1,i}(a) - \sum_{j=1}^n\beta_{ij}(a)\varphi_j\hat\psi_{1,i}(a)\right|\mathrm{d}a + 2\sum_{i=1}^n\int_0^{+\infty}\left|\sum_{j=1}^n\beta_{ij}(a)\varphi_j\hat\psi_{1,i}(a) - \sum_{j=1}^n\beta_{ij}(a)\hat\varphi_j\hat\psi_{1,i}(a)\right|\mathrm{d}a$$
$$+ \gamma^+\sum_{i=1}^n\int_0^{+\infty}\left|\psi_{2,i}(a) - \hat\psi_{2,i}(a)\right|\mathrm{d}a + p^+\sum_{i=1}^n|\varphi_i - \hat\varphi_i|$$
$$\le 2\beta^+C\sum_{i=1}^n\int_0^{+\infty}\left|\psi_{1,i}(a) - \hat\psi_{1,i}(a)\right|\mathrm{d}a + 2\beta^+C\sum_{j=1}^n\left|\varphi_j - \hat\varphi_j\right| + \gamma^+\sum_{i=1}^n\int_0^{+\infty}\left|\psi_{2,i}(a) - \hat\psi_{2,i}(a)\right|\mathrm{d}a + p^+\sum_{i=1}^n|\varphi_i - \hat\varphi_i|,$$

where $\gamma^+ := \max_{i\in\mathcal{N}}\left\{\gamma_i^+\right\}$, $p^+ := \max_{i\in\mathcal{N}}\{p_i\}$ and $\beta^+ := \max_{i,j\in\mathcal{N}}\left\{\beta_{ij}^+\right\}$. Hence, we can take $K(C) := \max\{2\beta^+C + p^+, \gamma^+\}$, then (3.4) directly follows. □

We next prove the following lemma on the boundedness of the solution.

Lemma 3.2. *For all $i \in \mathcal{N}$, we have $\limsup_{t\to+\infty} N_i(t) \le \Lambda_i/\mu_i$, where $N_i(t) := \int_0^{+\infty} S_i(t,a)\mathrm{d}a + U_{1i}(t) + \int_0^{+\infty} U_{2i}(t,a)\mathrm{d}a$.*

Proof. By integrating the first and third equations in (1.2), we have the following differential equations.

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\displaystyle\int_0^{+\infty} S_i(t,a)\mathrm{d}a = \Lambda_i - \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}a U_{1j}(t) - \mu_i \int_0^{+\infty} S_i(t,a)\mathrm{d}a, & t>0,\ i\in\mathcal{N},\\ \dfrac{\mathrm{d}U_{1i}(t)}{\mathrm{d}t} = \displaystyle\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}a U_{1j}(t) - (\mu_i+\delta_{1i}+p_i)\,U_{1i}(t) + \int_0^{+\infty}\gamma_i(a)U_{2i}(t,a)\mathrm{d}a, & t>0,\ i\in\mathcal{N},\\ \dfrac{\mathrm{d}}{\mathrm{d}t}\displaystyle\int_0^{+\infty} U_{2i}(t,a)\mathrm{d}a = pU_{1i}(t) - (\mu_i+\delta_{2i})\int_0^{+\infty} U_{2i}(t,a)\mathrm{d}a - \int_0^{+\infty}\gamma_i(a)U_{2i}(t,a)\mathrm{d}a, & t>0,\ i\in\mathcal{N}. \end{cases}$$

Adding up above equations yields

$$\frac{\mathrm{d}N_i(t)}{\mathrm{d}t} = \Lambda_i - \mu_i N_i(t) - \delta_{1i}U_{1i}(t) - \delta_{2i}\int_0^{+\infty} U_{2i}(t,a)\mathrm{d}a \le \Lambda_i - \mu_i N_i(t), \quad t>0,\ i\in\mathcal{N}. \tag{3.5}$$

Note that the positivity of U_{1i} and U_{2i}, $i\in\mathcal{N}$ is obvious from the form of system (1.2) and Assumption 1.1. From (3.5), we have $\limsup_{t\to+\infty} N_i(t) \le \Lambda_i/\mu_i$ for all $i\in\mathcal{N}$. □

From Lemmas 3.1-3.2 and the result in [23], we see that the following proposition holds on the existence and uniqueness of the integral solution of (3.2).

Proposition 3.1. *There exists a uniquely determined semiflow $\{\Phi(t)\}_{t\ge0}$ on $\mathbb{X}_{0,+}$ such that $\Phi(t)\mathbf{x}_0$ is the integral solution of* (3.2) *for any $\mathbf{x}_0 \in \mathbb{X}_{0,+}$, that is, $\int_0^t \Phi(s)\mathbf{x}_0\mathrm{d}s \in D(A)$ for all $t>0$, and $\Phi(t)\mathbf{x}_0 = \mathbf{x}_0 + A\int_0^t \Phi(s)\mathbf{x}_0\mathrm{d}s + \int_0^t F(\Phi(s)\mathbf{x}_0)\,\mathrm{d}s$ for all $t>0$.*

To investigate the differentiability of the integral solution $\Phi(t)\mathbf{x}_0$, we define the following set: $D(A_0) := \{\mathbf{x}\in D(A) : A\mathbf{x}+F(\mathbf{x}) \in \overline{D(A)}\}$. It can be shown as in [23, Proof of Theorem 6.3] that $D(A_0)\cap\mathbb{X}_{0,+}$ is dense in $\mathbb{X}_{0,+}$. The differentiability of the nonlinear operator F on $\mathbb{X}_0$ is obvious under Assumption 1.1. In fact, for any $\hat{\varrho} = \left(0_{\mathbb{R}^n}, \hat{\psi}_1, \hat{\varphi}, 0_{\mathbb{R}^n}, \hat{\psi}_2\right)^{\mathrm{T}} \in \mathbb{X}_0$, the differentiation of F at $\hat{\varrho}$ is given by the following linear operator.

$$F'[\hat{\varrho}]\begin{pmatrix}0_{\mathbb{R}^n}\\ \psi_1\\ \varphi\\ 0_{\mathbb{R}^n}\\ \psi_2\end{pmatrix} := \begin{pmatrix}0_{\mathbb{R}^n}\\ -\mathbf{B}(\hat{\varphi})(a)\psi_1(a) - \mathbf{B}(\varphi)(a)\hat{\psi}_1(a)\\ \int_0^{+\infty}\left\{\mathbf{B}(\hat{\varphi})(a)\psi_1(a)+\mathbf{B}(\varphi)(a)\hat{\psi}_1(a)\right\}\mathrm{d}a + \int_0^{+\infty}\mathbf{\Gamma}(a)\psi_2(a)\mathrm{d}a\\ \mathbf{P}\varphi\\ 0_{L^1(0,+\infty;\mathbb{R}^n)}\end{pmatrix}, \quad \begin{pmatrix}0_{\mathbb{R}^n}\\ \psi_1\\ \varphi\\ 0_{\mathbb{R}^n}\\ \psi_2\end{pmatrix} \in \mathbb{X}_0.$$

Hence, by using the result in [23, Section 4], we obtain the following proposition on the existence and uniqueness of the global classical solution of (3.2).

Proposition 3.2. *If $\mathbf{x}_0 \in D(A_0)\cap\mathbb{X}_{0,+}$, then the integral solution $\Phi(t)\mathbf{x}_0$ is continuously differentiable with respect to t, and $\mathbf{x}(t) := \Phi(t)\mathbf{x}_0$ is the global classical solution of the abstract Cauchy problem* (3.2).

4. Asymptotic smoothness of the semiflow

In this section, we prove the asymptotic smoothness of the semiflow $\{\Phi(t)\}_{t\ge0}$. To prove it, we will apply the following classical theorem (see, for instance, [24, Lemma 2.3.2] and [25, Theorem 2.46]).

Theorem 4.1. *The semiflow $\Phi : \mathbb{R}_+\times\mathbb{X}_{0,+} \to \mathbb{X}_{0,+}$ is asymptotically smooth if there are maps $\mathcal{W}_1, \mathcal{W}_2 : \mathbb{R}_+\times\mathbb{X}_{0,+} \to \mathbb{X}_{0,+}$ such that $\Phi(t)\mathbf{x}_0 = \mathcal{W}_1(t)\mathbf{x}_0 + \mathcal{W}_2(t)\mathbf{x}_0$, and the following hold for any bounded closed set Ω that is forward invariant under Φ: (i) $\liminf_{t\to\infty} \operatorname{diam}\mathcal{W}_1(t)(\Omega) = 0$; (ii) there exists a $t_\Omega \ge 0$ such that $\mathcal{W}_2(t)(\Omega)$ has a compact closure for each $t \ge t_\Omega$.*

To apply Theorem 4.1, we define $\mathcal{W}_1$ and $\mathcal{W}_2$ by

$$\mathcal{W}_1(t)\mathbf{x}_0 := \left(0_{\mathbb{R}^n}, \hat{\mathbf{S}}(t,\cdot), 0_{\mathbb{R}^n}, 0_{\mathbb{R}^n}, \hat{\mathbf{U}}_2(t,0)\right)^{\mathrm{T}} \quad \text{and} \quad \mathcal{W}_2(t)\mathbf{x}_0 := \left(0_{\mathbb{R}^n}, \tilde{\mathbf{S}}(t,\cdot), \mathbf{U}_1(t), 0_{\mathbb{R}^n}, \tilde{\mathbf{U}}_2(t,0)\right)^{\mathrm{T}},$$

where $\hat{\mathbf{S}}(t,\cdot) := \left(\hat{S}_1(t,\cdot), \cdots, \hat{S}_n(t,\cdot)\right)^{\mathrm{T}}$, $\tilde{\mathbf{S}}(t,\cdot) := \left(\tilde{S}_1(t,\cdot), \cdots, \tilde{S}_n(t,\cdot)\right)^{\mathrm{T}}$, $\hat{\mathbf{U}}_2(t,\cdot) := \left(\hat{U}_{21}(t,\cdot), \cdots, \hat{U}_{2n}(t,\cdot)\right)^{\mathrm{T}}$, $\tilde{\mathbf{U}}_2(t,\cdot) := \left(\tilde{U}_{21}(t,\cdot), \cdots, \tilde{U}_{2n}(t,\cdot)\right)^{\mathrm{T}}$ and, for all $i \in \mathcal{N}$,

$$\hat{S}_i(t,a) := \begin{cases} 0, & t-a>0, \\ S_i(t,a), & a-t \geq 0, \end{cases} \qquad \tilde{S}_i(t,a) := \begin{cases} S_i(t,a), & t-a>0, \\ 0, & a-t \geq 0, \end{cases}$$

$$\hat{U}_{2i}(t,a) := \begin{cases} 0, & t-a>0, \\ U_{2i}(t,a), & a-t \geq 0, \end{cases} \qquad \tilde{U}_{2i}(t,a) := \begin{cases} U_{2i}(t,a), & t-a>0, \\ 0, & a-t \geq 0. \end{cases}$$

Then, we see that $\Phi(t)\mathbf{x}_0 = \mathcal{W}_1(t)\mathbf{x}_0 + \mathcal{W}_2(t)\mathbf{x}_0$. We first verify the condition (i) in Theorem 4.1.

Lemma 4.1. $\mathcal{W}_1$ *satisfies the condition (i) in Theorem 4.1.*

Proof. Let $\Omega \subset D(A_0) \cap \mathbb{X}_{0,+}$ be any bounded closed set that is forward invariant under Φ. Let $C > 0$ be a positive constant such that $\|\varrho\|_{\mathbb{X}} < C$ holds for any $\varrho \in \Omega$. Let $\mathbf{x}_0 \in \Omega$. Integrating the equations of S_i and U_{2i} in (1.2) along the characteristic line $t - a =$ const., we have, for all $i \in \mathcal{N}$,

$$\hat{S}_i(t,a) := \begin{cases} 0, & t-a>0, \\ S_{i,0}(a-t)\,\mathrm{e}^{-\int_0^t \left\{\sum_{j=1}^n \beta_{ij}(a-t+\sigma)U_{1j}(\sigma)+\mu_i\right\}\mathrm{d}\sigma}, & a-t \geq 0, \end{cases} \quad \hat{U}_{2i}(t,a) := \begin{cases} 0, & t-a>0, \\ U_{2i,0}(a-t)\,\mathrm{e}^{-\int_0^t \{\mu_i+\delta_{2i}+\gamma_i(a-t+\sigma)\}\mathrm{d}\sigma}, & a-t \geq 0. \end{cases}$$

Hence, we have

$$\begin{aligned} \|\mathcal{W}_1(t)\mathbf{x}_0\|_{\mathbb{X}} &= \sum_{i=1}^n \int_0^{+\infty} \left|\hat{S}_i(t,a)\right| \mathrm{d}a + \sum_{i=1}^n \int_0^{+\infty} \left|\hat{U}_{2i}(t,a)\right| \mathrm{d}a \\ &= \sum_{i=1}^n \int_t^{+\infty} S_{i,0}(a-t)\,\mathrm{e}^{-\int_0^t \left\{\sum_{j=1}^n \beta_{ij}(a-t+\sigma)U_{1j}(\sigma)+\mu_i\right\}\mathrm{d}\sigma}\mathrm{d}a + \sum_{i=1}^n \int_t^{+\infty} U_{2i,0}(a-t)\,\mathrm{e}^{-\int_0^t \{\mu_i+\delta_{2i}+\gamma_i(a-t+\sigma)\}\mathrm{d}\sigma}\mathrm{d}a \\ &\leq \mathrm{e}^{-\mu^- t}\left(\sum_{i=1}^n \int_0^{+\infty} S_{i,0}(a)\,\mathrm{d}a + \sum_{i=1}^n \int_0^{+\infty} U_{2i,0}(a)\,\mathrm{d}a\right) = \mathrm{e}^{-\mu^- t}\|\mathbf{x}_0\|_{\mathbb{X}} < \mathrm{e}^{-\mu^- t} C \to 0 \text{ as } t \to +\infty. \end{aligned}$$

Hence, $\liminf_{t\to\infty} \operatorname{diam} \mathcal{W}_1(t)(\Omega) = 0$ and (i) is satisfied □

We next verify the condition (ii) in Theorem 4.1.

Lemma 4.2. $\mathcal{W}_2$ *satisfies the condition (ii) in Theorem 4.1.*

Proof. Let Ω be as in the proof of Lemma 4.1. Without loss of generality, we can assume that $C > \max_{i\in\mathcal{N}} \Lambda_i/\mu_i$. Then, from Lemma 3.2, we see that $U_{1i}(t)$, $i \in \mathcal{N}$ remains in the compact set $[0, C]$. In what follows, we prove that $\tilde{S}_i(t,\cdot)$ and $\tilde{U}_{2i}(t,\cdot)$, $i \in \mathcal{N}$ remain in precompact subsets of $\mathbb{X}_{0,+}$, which is independent of $\mathbf{x}_0 \in \Omega$. By integrating the equations of S_i and U_{2i} in (1.2) along the characteristic line $t - a =$ const., we have

$$\tilde{S}_i(t,a) := \begin{cases} \Lambda_i \mathrm{e}^{-\int_0^a \left\{\sum_{j=1}^n \beta_{ij}(\sigma)U_{1j}(t-a+\sigma)+\mu_i\right\}\mathrm{d}\sigma}, & t-a>0, \\ 0, & a-t \geq 0, \end{cases} \quad i \in \mathcal{N} \tag{4.1}$$

and

$$\tilde{U}_{2i}(t,a) := \begin{cases} p_i U_{1i}(t-a)\mathrm{e}^{-\int_0^a \{\mu_i+\delta_{2i}+\gamma_i(\sigma)\}\mathrm{d}\sigma}, & t-a>0, \\ 0, & a-t \geq 0, \end{cases} \quad i \in \mathcal{N}. \tag{4.2}$$

Hence, we have $0 \leq \tilde{S}_i(t,a) \leq \Lambda_i \mathrm{e}^{-\mu_i a}$ and $0 \leq \tilde{U}_{2i}(t,a) \leq p_i C \mathrm{e}^{-\mu_i a}$ for all $i \in \mathcal{N}$. From these inequalities, we see that for any initial data $\mathbf{x}_0 \in \Omega$, $\sum_{i=1}^n \int_0^{+\infty} \tilde{S}_i(t,a)\mathrm{d}a \leq \sum_{i=1}^n \Lambda_i/\mu_i < +\infty$ and $\sum_{i=1}^n \int_0^{+\infty} \tilde{U}_{2i}(t,a)\mathrm{d}a \leq \sum_{i=1}^n p_i C/\mu_i < +\infty$. Furthermore, the following convergences hold uniformly in $\mathbf{x}_0 \in \Omega$:

$$0 \le \sum_{i=1}^{n} \int_{h}^{+\infty} \tilde{S}_i(t,a)\mathrm{d}a \le \sum_{i=1}^{n} \frac{\Lambda_i}{\mu_i} \mathrm{e}^{-\mu_i h} \to 0 \quad \text{as} \quad h \to +\infty, \quad 0 \le \sum_{i=1}^{n} \int_{h}^{+\infty} \tilde{U}_{2i}(t,a)\mathrm{d}a \le \sum_{i=1}^{n} \frac{p_i C}{\mu_i} \mathrm{e}^{-\mu_i h} \to 0 \quad \text{as} \quad h \to +\infty,$$

$$0 \le \sum_{i=1}^{n} \int_{0}^{h} \tilde{S}_i(t,a)\mathrm{d}a \le \sum_{i=1}^{n} \frac{\Lambda_i}{\mu_i} \left(1 - \mathrm{e}^{-\mu_i h}\right) \to 0 \quad \text{as} \quad h \to 0+, \quad 0 \le \sum_{i=1}^{n} \int_{0}^{h} \tilde{U}_{2i}(t,a)\mathrm{d}a \le \sum_{i=1}^{n} \frac{p_i C}{\mu_i} \left(1 - \mathrm{e}^{-\mu_i h}\right) \to 0 \quad \text{as} \quad h \to 0+.$$

Hence, to complete the proof, we have to show the following convergences, which are uniform in $\mathbf{x}_0 \in \Omega$ (see [25, Theorem B.2]).

$$\lim_{h \to 0+} \sum_{i=1}^{n} \int_{0}^{+\infty} \left| \tilde{S}_i(t, a+h) - \tilde{S}_i(t,a) \right| \mathrm{d}a = 0, \quad \lim_{h \to 0+} \sum_{i=1}^{n} \int_{0}^{+\infty} \left| \tilde{U}_{2i}(t, a+h) - \tilde{U}_{2i}(t,a) \right| \mathrm{d}a = 0. \tag{4.3}$$

To prove (4.3), without loss of generality, we can assume that h is sufficiently small such that $0 < h < t$. Then, from (4.1), we have

$$\begin{aligned}
&\sum_{i=1}^{n} \int_{0}^{+\infty} \left| \tilde{S}_i(t, a+h) - \tilde{S}_i(t,a) \right| \mathrm{d}a = \sum_{i=1}^{n} \int_{0}^{t-h} \left| \tilde{S}_i(t, a+h) - \tilde{S}_i(t,a) \right| \mathrm{d}a + \sum_{i=1}^{n} \int_{t-h}^{t} \left| 0 - \tilde{S}_i(t,a) \right| \mathrm{d}a \\
&\le \sum_{i=1}^{n} \int_{0}^{t-h} \Lambda_i \left| \mathrm{e}^{-\int_0^{a+h} \left\{ \sum_{j=1}^{n} \beta_{ij}(\sigma) U_{1j}(t-a-h+\sigma) + \mu_i \right\} \mathrm{d}\sigma} - \mathrm{e}^{-\int_0^{a} \left\{ \sum_{j=1}^{n} \beta_{ij}(\sigma) U_{1j}(t-a+\sigma) + \mu_i \right\} \mathrm{d}\sigma} \right| \mathrm{d}a + \sum_{i=1}^{n} \Lambda_i h \\
&\le \sum_{i=1}^{n} \int_{0}^{t-h} \Lambda_i \left| \int_0^{a+h} \left\{ \sum_{j=1}^{n} \beta_{ij}(\sigma) U_{1j}(t-a-h+\sigma) + \mu_i \right\} \mathrm{d}\sigma - \int_0^{a} \left\{ \sum_{j=1}^{n} \beta_{ij}(\sigma) U_{1j}(t-a+\sigma) + \mu_i \right\} \mathrm{d}\sigma \right| \mathrm{d}a + \sum_{i=1}^{n} \Lambda_i h \\
&\le \sum_{i=1}^{n} \int_{0}^{t-h} \Lambda_i \sum_{j=1}^{n} \beta_{ij}^{+} \left(Ch + \int_0^a \left| U_{1j}(t-a-h+\sigma) - U_{1j}(t-a+\sigma) \right| \mathrm{d}\sigma \right) \mathrm{d}a + \sum_{i=1}^{n} \Lambda_i h \left\{ 1 + \mu_i (t-h) \right\},
\end{aligned} \tag{4.4}$$

where we have used the relation $|\mathrm{e}^{-x} - \mathrm{e}^{-y}| \le |x - y|$. Similarly, from (4.2), we have

$$\begin{aligned}
&\sum_{i=1}^{n} \int_{0}^{+\infty} \left| \tilde{U}_{2i}(t, a+h) - \tilde{U}_{2i}(t,a) \right| \mathrm{d}a = \sum_{i=1}^{n} \int_{0}^{t-h} \left| \tilde{U}_{2i}(t, a+h) - \tilde{U}_{2i}(t,a) \right| \mathrm{d}a + \sum_{i=1}^{n} \int_{t-h}^{t} \left| 0 - \tilde{U}_{2i}(t,a) \right| \mathrm{d}a \\
&\le \sum_{i=1}^{n} \int_{0}^{t-h} p_i \left| U_{1i}(a+h-t) \mathrm{e}^{-\int_0^{a+h} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma} - U_{1i}(a-t) \mathrm{e}^{-\int_0^{a} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma} \right| \mathrm{d}a + \sum_{i=1}^{n} p_i C h \\
&\le \sum_{i=1}^{n} \int_{0}^{t-h} p_i \left| U_{1i}(a+h-t) \mathrm{e}^{-\int_0^{a+h} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma} - U_{1i}(a-t) \mathrm{e}^{-\int_0^{a+h} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma} \right| \mathrm{d}a \\
&\quad + \sum_{i=1}^{n} \int_{0}^{t-h} p_i \left| U_{1i}(a-t) \mathrm{e}^{-\int_0^{a+h} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma} - U_{1i}(a-t) \mathrm{e}^{-\int_0^{a} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma} \right| \mathrm{d}a + \sum_{i=1}^{n} p_i C h \\
&\le \sum_{i=1}^{n} \int_{0}^{t-h} p_i \left| U_{1i}(a+h-t) - U_{1i}(a-t) \right| \mathrm{d}a + \sum_{i=1}^{n} \int_{0}^{t-h} p_i C \left| \int_0^{a+h} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma - \int_0^{a} \{\mu_i + \delta_{2i} + \gamma_i(\sigma)\} \mathrm{d}\sigma \right| \mathrm{d}a + \sum_{i=1}^{n} p_i C h \\
&\le \sum_{i=1}^{n} \int_{0}^{t-h} p_i \left| U_{1i}(a+h-t) - U_{1i}(a-t) \right| \mathrm{d}a + \sum_{i=1}^{n} p_i C h \left\{ 1 + (\mu_i + \delta_{2i} + \gamma_i^{+})(t-h) \right\}.
\end{aligned} \tag{4.5}$$

Now, from the second equation in (1.2), we have $U_{1i}'(t) \le \sum_{j=1}^{n} \beta_{ij}^{+} C^2 + (\mu_i + \delta_{1i} + p_i) C + \gamma_i^{+} C =: M_i$ for all $t > 0$ and $i \in \mathcal{N}$. Hence, U_{1i} is Lipschitz continuous on $\mathbb{R}_+$ with Lipschitz coefficient M_i, $i \in \mathcal{N}$. Then, from (4.4) and (4.5), we have

$$\sum_{i=1}^{n} \int_{0}^{+\infty} \left| \tilde{S}_i(t, a+h) - \tilde{S}_i(t,a) \right| \mathrm{d}a \le \sum_{i=1}^{n} \Lambda_i \sum_{j=1}^{n} \beta_{ij}^{+} \left(Ch(t-h) + M_j h \frac{(t-h)^2}{2} \right) + \sum_{i=1}^{n} \Lambda_i h \left\{ 1 + \mu_i (t-h) \right\} \to 0 \quad \text{as} \quad h \to 0+,$$

$$\sum_{i=1}^{n} \int_{0}^{+\infty} \left| \tilde{U}_{2i}(t, a+h) - \tilde{U}_{2i}(t,a) \right| \mathrm{d}a \le \sum_{i=1}^{n} p_i M_i h (t-h) + \sum_{i=1}^{n} p_i C h \left\{ 1 + (\mu_i + \delta_{2i} + \gamma_i^{+})(t-h) \right\} \to 0 \quad \text{as} \quad h \to 0+.$$

Hence, (4.3) is shown and the proof is complete. □

From Lemmas 4.1 and 4.2, we can apply Theorem 4.1 to obtain the following proposition on the asymptotic smoothness of the semiflow $\{\Phi(t)\}_{t\geq 0}$.

Proposition 4.1. *The semiflow $\{\Phi(t)\}_{t\geq 0}$ defined as in Proposition 3.1 is asymptotically smooth.*

By virtue of Proposition 4.1, we can apply the invariance principle (see [26, Theorem 4.2 in Chapter IV]) to show the global asymptotic stability of each equilibrium of system (1.2). We define the following sets.

$$C := \left\{ \mathbf{x} = (0_{\mathbb{R}^n}, \psi_1, \varphi, 0_{\mathbb{R}^n}, \psi_2)^{\mathrm{T}} \in D(A_0) \cap \mathbb{X}_{0,+} : \int_0^{+\infty} \psi_{1,i}(a)\mathrm{d}a + \varphi_i + \int_0^{+\infty} \psi_{2,i}(a)\mathrm{d}a \leq \frac{\Lambda_i}{\mu_i} \text{ for all } i \in \mathcal{N} \right\},$$
$$C_0 := \left\{ \mathbf{x} = (0_{\mathbb{R}^n}, \psi_1, \varphi, 0_{\mathbb{R}^n}, \psi_2)^{\mathrm{T}} \in C : \varphi_i > 0 \text{ for some } i \in \mathcal{N} \text{ or } \psi_{2,i}(a) > 0 \text{ for some } a \geq 0 \text{ and } i \in \mathcal{N} \right\}, \quad \partial C := C \setminus C_0.$$

By Assumption 1.1 and Lemma 3.2, we can prove the following lemma.

Lemma 4.3. (i) $\Phi(t)(C) \subset C$ *for all* $t > 0$. (ii) $\Phi(t)(\partial C) \subset \partial C$ *for all* $t > 0$. (iii) $\Phi(t)(C_0) \subset C_0$ *for all* $t > 0$.

Proof. (i) By (3.5) in the proof of Lemma 3.2, we have $N_i(t) \leq N_i(0)\mathrm{e}^{-\mu_i t} + (1-\mathrm{e}^{-\mu_i t})\Lambda_i/\mu_i = \Lambda_i/\mu_i + (N_i(0) - \Lambda_i/\mu_i)\,\mathrm{e}^{-\mu_i t}$ for all $t > 0$ and $i \in \mathcal{N}$. Hence, if $N_i(0) \leq \Lambda_i/\mu_i$ for all $i \in \mathcal{N}$, then $N_i(t) \leq \Lambda_i/\mu_i$ for all $t > 0$ and $i \in \mathcal{N}$. This implies that $\Phi(t)(C) \subset C$ for all $t > 0$.

(ii) Integrating the second and third equations in (1.2), we have, for all $i \in \mathcal{N}$,

$$U_{1i}(t) = U_{1i,0}\mathrm{e}^{-(\mu_i+\delta_{1i}+p_i)t} + \int_0^t \mathrm{e}^{-(\mu_i+\delta_{1i}+p_i)(t-u)} \left(\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a) S_i(u,a)\mathrm{d}a U_{1j}(u) + \int_0^{+\infty} \gamma_i(a) U_{2i}(u,a)\mathrm{d}a \right) \mathrm{d}u, \quad t > 0, \tag{4.6}$$

and

$$U_{2i}(t,a) = \begin{cases} p_i U_{1i}(t-a)\mathrm{e}^{-\int_0^a (\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}, & t-a > 0, \\ U_{2i,0}(a-t)\,\mathrm{e}^{-\int_0^t (\mu_i+\delta_{2i}+\gamma_i(a-t+\sigma))\mathrm{d}\sigma}, & a-t \geq 0. \end{cases} \tag{4.7}$$

respectively. Suppose that $\mathbf{x}_0 \in \partial C$. We then have $U_{1i,0} = 0$ and $U_{2i,0}(a) = 0$ for all $a \geq 0$ and $i \in \mathcal{N}$. From (4.6)-(4.7) and the continuity, we see that $U_{1i}(t) = 0$ and $U_{2i}(t,a) = 0$ for all $t > 0$, $a \geq 0$ and $i \in \mathcal{N}$. This implies that $\Phi(t)(\partial C) \subset \partial C$ for all $t > 0$.

(iii) If $U_{1i,0} > 0$ for some $i \in \mathcal{N}$, then it follows from (4.6) that $U_{1i}(t) \geq U_{1i,0}\mathrm{e}^{-(\mu_i+\delta_{1i}+p_i)t} > 0$ for all $t > 0$, which implies that $\Phi(t)\mathbf{x}_0 \in C_0$ for all $t > 0$. If $U_{2i,0}(a) > 0$ for some $a \geq 0$ and $i \in \mathcal{N}$, then it follows from the continuity (note that $\mathbf{U}_{2,0} \in W^{1,1}(0,+\infty;\mathbb{R}^n)$) that there exists a nonempty interval $(a_1, a_2) \subset (0,+\infty)$ such that $U_{2i,0}(a) > 0$ for all $a \in (a_1, a_2)$. Then, from the last term in (4.6) and the continuity, it follows again that $U_{1i}(t) > 0$ for all $t > 0$, which implies that $\Phi(t)\mathbf{x}_0 \in C_0$ for all $t > 0$. This completes the proof. □

In what follows, we use the following notations to denote the drug-free and drug-endemic equilibria in C.

$$\tilde{E}^0 := \left(0_{\mathbb{R}^n}, S_1^0(\cdot), \cdots, S_n^0(\cdot), 0_{\mathbb{R}^n}, 0_{\mathbb{R}^n}, 0_{L^1(0,+\infty;\mathbb{R}^n)}\right)^T \in C,$$
$$\tilde{E}^* := \left(0_{\mathbb{R}^n}, S_1^*(\cdot), \cdots, S_n^*(\cdot), U_{11}^*, \cdots, U_{1n}^*, 0_{\mathbb{R}^n}, U_{21}^*(\cdot), \cdots, U_{2n}^*(\cdot)\right)^T \in C.$$

5. Global asymptotic stability of the drug-free equilibrium

In this section, we prove the global asymptotic stability of the drug-free equilibrium $\tilde{E}^0$ in C when $\mathfrak{R}_0 < 1$. On the local asymptotic stability of $\tilde{E}^0$, we prove the following proposition.

Proposition 5.1. *Suppose that $\mathfrak{R}_0 \leq 1$. The drug-free equilibrium $\tilde{E}^0$ is locally asymptotically stable.*

Proof. The second and third equations in (1.2) can be linearized around the drug-free equilibrium $\tilde{E}^0$ as follows.

$$\begin{cases} \dfrac{\mathrm{d}U_{1i}(t)}{\mathrm{d}t} = \displaystyle\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a) S_i^0(a)\mathrm{d}a U_{1j}(t) - (\mu_i + \delta_{1i} + p_i)\, U_{1i}(t) + \int_0^{+\infty} \gamma_i(a) U_{2i}(t,a)\mathrm{d}a, & t > 0,\ i \in \mathcal{N}, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a} \right) U_{2i}(t,a) = -\left(\mu_i + \delta_{2i} + \gamma_i(a)\right) U_{2i}(t,a), & t > 0,\ a > 0,\ i \in \mathcal{N}, \\ U_{2i}(t,0) = p_i U_{1i}(t), & t > 0,\ i \in \mathcal{N}. \end{cases} \tag{5.1}$$

Substituting $U_{1i}(t) = u_{1i}\mathrm{e}^{\lambda t}$ and $U_{2i}(t,a) = u_{2i}(a)\mathrm{e}^{\lambda t}$, $i \in \mathcal{N}$, $\lambda \in \mathbb{C}$ into each equation in (5.1) and dividing both sides of each equation by $\mathrm{e}^{\lambda t}$, we have

$$\begin{cases} \lambda u_{1i} = \sum_{j=1}^{n} \int_0^{+\infty} \beta_{ij}(a) S_i^0(a) \mathrm{d}a u_{1j} - (\mu_i + \delta_{1i} + p_i) u_{1i} + \int_0^{+\infty} \gamma_i(a) u_{2i}(a) \mathrm{d}a, & i \in \mathcal{N}, \\ \left(\lambda + \frac{\mathrm{d}}{\mathrm{d}a}\right) u_{2i}(a) = -(\mu_i + \delta_{2i} + \gamma_i(a)) u_{2i}(a), & a > 0, \ i \in \mathcal{N}, \\ u_{2i}(0) = p_i u_{1i}, & i \in \mathcal{N}. \end{cases} \tag{5.2}$$

From the second and third equations in (5.2), we have

$$u_{2i}(a) = p_i u_{1i} \mathrm{e}^{-\int_0^a (\lambda + \mu_i + \delta_{2i} + \gamma_i(\sigma)) \mathrm{d}\sigma} = p_i \mathrm{e}^{-\lambda a} \varrho_i(a) u_{1i}, \quad a \geq 0, \ i \in \mathcal{N}. \tag{5.3}$$

Substituting (5.3) into the first equation in (5.2), we have

$$\lambda u_{1i} = \sum_{j=1}^{n} \int_0^{+\infty} \beta_{ij}(a) S_i^0(a) \mathrm{d}a \, u_{1j} - (\mu_i + \delta_{1i} + p_i) u_{1i} + p_i \int_0^{+\infty} \gamma_i(a) \mathrm{e}^{-\lambda a} \varrho_i(a) \mathrm{d}a \, u_{1i}, \quad i \in \mathcal{N}.$$

Let $\lambda := x + iy$, $x, y \in \mathbb{R}$. Comparing the real parts of both sides, we have

$$x u_{1i} = \sum_{j=1}^{n} \int_0^{+\infty} \beta_{ij}(a) S_i^0(a) \mathrm{d}a \, u_{1j} - (\mu_i + \delta_{1i} + p_i) u_{1i} + p_i \int_0^{+\infty} \gamma_i(a) \mathrm{e}^{-xa} \cos(ya) \varrho_i(a) \mathrm{d}a \, u_{1i}, \quad i \in \mathcal{N}.$$

This equation can be arranged as follows.

$$u_{1i} = \frac{\sum_{j=1}^{n} \int_0^{+\infty} \beta_{ij}(a) S_i^0(a) \mathrm{d}a \, u_{1j}}{x + \mu_i + \delta_{1i} + \left(1 - \int_0^{+\infty} \gamma_i(a) \mathrm{e}^{-xa} \cos(ya) \varrho_i(a) \mathrm{d}a\right) p_i}, \quad i \in \mathcal{N}.$$

By using the matrix-vector form, we have

$$\mathbf{u}_1 = \tilde{M}^0(x,y)\mathbf{u}_1, \quad \mathbf{u}_1 := (u_{1i})_{i \in \mathcal{N}}, \quad \tilde{M}^0(x,y) := \left(\frac{\sum_{j=1}^{n} \int_0^{+\infty} \beta_{ij}(a) S_i^0(a) \mathrm{d}a}{x + \mu_i + \delta_{1i} + \left(1 - \int_0^{+\infty} \gamma_i(a) \mathrm{e}^{-xa} \cos(ya) \varrho_i(a) \mathrm{d}a\right) p_i} \right)_{i,j \in \mathcal{N}}. \tag{5.4}$$

Suppose that $x \geq 0$. Since $\int_0^{+\infty} \gamma_i(a) \mathrm{e}^{-xa} \cos(ya) \varrho_i(a) \mathrm{d}a \leq \theta_i < 1$ for all $i \in \mathcal{N}$ and $y \in \mathbb{R}$, matrix $\tilde{M}^0(x,y)$ is nonnegative and irreducible. Hence, from the Perron-Frobenius theorem ([21]) and the first equation in (5.4), we see that $r(\tilde{M}^0(x,y)) = 1$ for all $x \geq 0$ and $y \in \mathbb{R}$. Moreover, since $\tilde{M}^0(x,y) < M^0$ for all $x \geq 0$ and $y \in \mathbb{R}$, it follows again from the Perron-Frobenius theorem that $1 = r(\tilde{M}^0(x,y)) < r(M^0) = \mathfrak{R}_0$ for all $x \geq 0$ and $y \in \mathbb{R}$. This is a contradiction to $\mathfrak{R}_0 \leq 1$, and thus, $x < 0$, which implies that $\tilde{E}^0$ is locally asymptotically stable. This completes the proof. □

To construct suitable Lyapunov functions, we will use the following Volterra-type function (see, e.g., [27, 28]): $G(z) = z - 1 - \ln z$, $z > 0$. It is easy to see that $G(z) \geq 0$ for all $z > 0$ and $G(z) = 0$ if and only if $z = 1$. In the Lyapunov function stated below, we use the following function.

$$L_{1i}(t) := \int_0^{+\infty} S_i^0(a) G\left(\frac{S_i(t,a)}{S_i^0(a)}\right) \mathrm{d}a, \quad t > 0, \ i \in \mathcal{N}. \tag{5.5}$$

To make this function finite, we need the following additional assumption on the initial data $S_{i,0}(a)$, $i \in \mathcal{N}$.

Assumption 5.1. *For all $i \in \mathcal{N}$, we have $\int_0^{+\infty} \left|\ln S_{i,0}(a)\right| \mathrm{e}^{-\mu_i a} \mathrm{d}a < +\infty$.*

In fact, since $S_i(t,a)$ has a structure comparable with $\Lambda_i \mathrm{e}^{-\mu_i a}$ for $t - a > 0$, and $|\ln(\Lambda \mathrm{e}^{-\mu_i a})| \mathrm{e}^{-\mu_i a}$ is integrable, Assumption 5.1 seems mathematically natural. Biologically, in the initial invasion phase of the heroin epidemic, we can assume that there are very few drug users, and thus, the age distribution $S_{i,0}(a)$ of susceptible individuals in group $i \in \mathcal{N}$ is thought to be almost equal to $S_i^0(a) = \Lambda_i \mathrm{e}^{-\mu_i a}$, and Assumption 5.1 holds. Under Assumption 5.1, we have the following lemma.

Lemma 5.1. *Let Assumption 5.1 be satisfied. $L_{1i}(t)$ is finite for all $t > 0$ and $i \in \mathcal{N}$.*

Proof. By integrating the equations of S_i, $i \in \mathcal{N}$ in (1.2) along the characteristic line $t - a =$ const., we have

$$
\begin{aligned}
&\left| S_i^0(a) \ln \frac{S_i(t,a)}{S_i^0(a)} \right| = \left| S_i^0(a) \ln S_i(t,a) - S_i^0(a) \ln S_i^0(a) \right| \\
&\le \begin{cases} \left| \Lambda_i e^{-\mu_i a} \ln \left(\Lambda_i e^{-\int_0^a \left(\sum_{j=1}^n \beta_{ij}(\sigma) U_{1j}(t-a+\sigma) + \mu_i \right) d\sigma} \right) \right| + \left| \Lambda_i e^{-\mu_i a} \ln \left(\Lambda_i e^{-\mu_i a} \right) \right|, & t - a > 0, \\ \left| \Lambda_i e^{-\mu_i a} \ln \left(S_{i,0}(a-t) e^{-\int_0^t \left(\sum_{j=1}^n \beta_{ij}(a-t+\sigma) U_{1j}(\sigma) + \mu_i \right) d\sigma} \right) \right| + \left| \Lambda_i e^{-\mu_i a} \ln \left(\Lambda_i e^{-\mu_i a} \right) \right|, & a - t \ge 0 \end{cases} \\
&= \begin{cases} \left| \Lambda_i e^{-\mu_i a} \ln \Lambda_i - \Lambda_i e^{-\mu_i a} \int_0^a \left(\sum_{j=1}^n \beta_{ij}(\sigma) U_{1j}(t-a+\sigma) + \mu_i \right) d\sigma \right| + \left| \Lambda_i e^{-\mu_i a} \ln \Lambda_i - \Lambda_i e^{-\mu_i a} \mu_i a \right|, & t - a > 0, \\ \left| \Lambda_i e^{-\mu_i a} \ln S_{i,0}(a-t) - \Lambda_i e^{-\mu_i a} \int_0^t \left(\sum_{j=1}^n \beta_{ij}(a-t+\sigma) U_{1j}(\sigma) + \mu_i \right) d\sigma \right| + \left| \Lambda_i e^{-\mu_i a} \ln \Lambda_i - \Lambda_i e^{-\mu_i a} \mu_i a \right|, & a - t \ge 0 \end{cases} \\
&\le \begin{cases} 2\Lambda_i \left| \ln \Lambda_i \right| e^{-\mu_i a} + \Lambda_i e^{-\mu_i a} \left(\sum_{j=1}^n \beta_{ij}^+ \frac{\Lambda_j}{\mu_j} + 2\mu_i \right) a, & t - a > 0, \\ \Lambda_i \left| \ln S_{i,0}(a-t) \right| e^{-\mu_i a} + \Lambda_i \left| \ln \Lambda_i \right| e^{-\mu_i a} + \Lambda_i e^{-\mu_i a} \left(\sum_{j=1}^n \beta_{ij}^+ \frac{\Lambda_i}{\mu_i} + 2\mu_i \right) a, & a - t \ge 0, \end{cases} \quad i \in \mathcal{N}.
\end{aligned}
$$

Hence, from Lemma 3.2, we have

$$
\begin{aligned}
&\int_0^{+\infty} \left| S_i^0(a) \ln \frac{S_i(t,a)}{S_i^0(a)} \right| da = \int_0^t \left| S_i^0(a) \ln \frac{S_i(t,a)}{S_i^0(a)} \right| da + \int_t^{+\infty} \left| S_i^0(a) \ln \frac{S_i(t,a)}{S_i^0(a)} \right| da \\
&\le \Lambda_i \left| \ln \Lambda_i \right| \int_0^t e^{-\mu_i a} da + \Lambda_i \int_t^{+\infty} \left| \ln S_{i,0}(a-t) \right| e^{-\mu_i a} da + \int_0^{+\infty} \left[\Lambda_i \left| \ln \Lambda_i \right| e^{-\mu_i a} + \Lambda_i e^{-\mu_i a} \left(\sum_{j=1}^n \beta_{ij}^+ \frac{\Lambda_i}{\mu_i} + 2\mu_i \right) a \right] da \\
&= \frac{\Lambda_i \left| \ln \Lambda_i \right|}{\mu_i} (1 - e^{-\mu_i t}) + \Lambda_i \int_0^{+\infty} \left| \ln S_{i,0}(a) \right| e^{-\mu_i (a+t)} da + \frac{\Lambda_i \left| \ln \Lambda_i \right|}{\mu_i} + \frac{\Lambda_i}{\mu_i^2} \left(\sum_{j=1}^n \beta_{ij}^+ \frac{\Lambda_i}{\mu_i} + 2\mu_i \right) \\
&\le 2 \frac{\Lambda_i \left| \ln \Lambda_i \right|}{\mu_i} + \Lambda_i \int_0^{+\infty} \left| \ln S_{i,0}(a) \right| e^{-\mu_i a} da + \frac{\Lambda_i}{\mu_i^2} \left(\sum_{j=1}^n \beta_{ij}^+ \frac{\Lambda_i}{\mu_i} + 2\mu_i \right), \quad t > 0, \ i \in \mathcal{N}.
\end{aligned}
$$

Under Assumption 5.1, the last expression in the above inequality is finite. Hence, from Lemma 3.2, we have

$$
L_{1i}(t) \le |L_{1i}(t)| \le \int_0^{+\infty} \left| S_i^0(a) G\left(\frac{S_i(t,a)}{S_i^0(a)} \right) \right| da \le \int_0^{+\infty} \left(S_i(t,a) + S_i^0(a) + \left| S_i^0(a) \ln \frac{S_i(t,a)}{S_i^0(a)} \right| \right) da < +\infty, \quad t > 0, \ i \in \mathcal{N}.
$$

This completes the proof. □

In the Lyapunov function below, we also use the following function.

$$
L_{2i}(t) := \int_0^{+\infty} \zeta_i(a) U_{2i}(t,a) da, \quad t > 0, \ i \in \mathcal{N}, \tag{5.6}
$$

where

$$
\zeta_i(a) = \int_a^{+\infty} \gamma_i(s) e^{-\int_a^s \alpha_i(\sigma) d\sigma} ds, \quad a > 0, \ i \in \mathcal{N} \tag{5.7}
$$

(see [29, Proof of Theorem 9.5] for similar functions). Note that $\zeta_i(a) \in (0,1)$ for $0 < a < +\infty$ and $\zeta_i(0) = \theta_i$. The derivative of $\zeta_i(a)$ satisfies $\zeta_i'(a) = \zeta_i(a)\alpha_i(a) - \gamma_i(a)$ for all $a \ge 0$ and $i \in \mathcal{N}$. Using functions L_{1i} and L_{2i}, we construct a suitable Lyapunov function to prove the following theorem on the global asymptotic stability of the drug-free equilibrium.

Theorem 5.1. *Suppose that $\mathfrak{R}_0 < 1$ and Assumption 5.1 holds. The drug-free equilibrium $\tilde{E}^0$ of system (1.2) is globally asymptotically stable in $\mathcal{C}$.*

Proof. Since matrix M^0 is nonnegative and irreducible, we can use the Perron-Frobenius theorem (see [21]) to find that M^0 has a strictly positive left eigenvector $(\omega_1, \omega_2, \cdots, \omega_n)$ corresponding to the eigenvalue $\Re_0 = \rho(M^0) \leq 1$. Let $c_i := \omega_i / (\mu_i + \delta_{1i} + (1-\theta_i)p_i)$ for all $i \in \mathcal{N}$, and construct the following Lyapunov function: $V_0(\mathbf{x}(t)) := \sum_{i=1}^n c_i \left[L_{1i}(t) + U_{1i}(t) + L_{2i}(t)\right]$, $t > 0$, where $L_{1i}(t)$ and $L_{2i}(t)$ are defined by (5.5) and (5.6), respectively. By virtue of Lemmas 4.3 and 5.1, the Lyapunov function $V_0(\mathbf{x}(t))$ is finite for all $t > 0$, provided $\mathbf{x}_0 \in C$ and Assumption 5.1 holds.

The derivative of $L_{1i}(t)$ along the solution trajectory of system (1.2) is calculated as follows.

$$L_{1i}'(t) = \int_0^{+\infty} S_i^0(a)\left(1 - \frac{S_i^0(a)}{S_i(t,a)}\right)\frac{1}{S_i^0(a)}\frac{\partial S_i(t,a)}{\partial t}\mathrm{d}a = -\int_0^{+\infty} S_i^0(a)\left(\frac{S_i(t,a)}{S_i^0(a)} - 1\right)\left(\frac{\partial_a S_i(t,a)}{S_i(t,a)} + \mu_i + \sum_{j=1}^n \beta_{ij}(a)U_{1j}(t)\right)\mathrm{d}a, \quad i \in \mathcal{N},$$

where ∂_a denotes $\partial/\partial a$. Recalling that $\mathrm{d}S_i^0(a)/\mathrm{d}a = -\mu_i S_i^0(a)$, it follows that

$$\frac{\partial}{\partial a}G\left(\frac{S_i(t,a)}{S_i^0(a)}\right) = \left(\frac{S_i(t,a)}{S_i^0(a)} - 1\right)\left(\frac{\partial_a S_i(t,a)}{S_i(t,a)} + \mu_i\right), \quad i \in \mathcal{N}.$$

Hence, using integration by parts, we have, for all $i \in \mathcal{N}$,

$$\begin{aligned}
L_{1i}'(t) &= -\int_0^{+\infty} S_i^0(a)\frac{\partial}{\partial a}G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\mathrm{d}a - \int_0^{+\infty} S_i^0(a)\left(\frac{S_i(t,a)}{S_i^0(a)} - 1\right)\sum_{j=1}^n \beta_{ij}(a)U_{1j}(t)\mathrm{d}a \\
&= -S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\Bigg|_{a=0}^{a=+\infty} + \int_0^{+\infty} G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\frac{\mathrm{d}S_i^0(a)}{\mathrm{d}a}\mathrm{d}a - \int_0^{+\infty} S_i(t,a)\sum_{j=1}^n \beta_{ij}(a)U_{1j}(t)\mathrm{d}a + \int_0^{+\infty} S_i^0(a)\sum_{j=1}^n \beta_{ij}(a)U_{1j}(t)\mathrm{d}a \\
&= -S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\Bigg|^{a=+\infty} + S_i^0(0)G\left(\frac{S_i(t,0)}{S_i^0(0)}\right) - \int_0^{+\infty} \mu_i S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\mathrm{d}a \\
&\quad - \int_0^{+\infty}\sum_{j=1}^n \beta_{ij}(a)S_i(t,a)U_{1j}(t)\mathrm{d}a + \int_0^{+\infty}\sum_{j=1}^n \beta_{ij}(a)S_i^0(a)U_{1j}(t)\mathrm{d}a \\
&= -S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\Bigg|^{a=+\infty} - \int_0^{+\infty} \mu_i S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\mathrm{d}a - \int_0^{+\infty}\sum_{j=1}^n \beta_{ij}(a)S_i(t,a)U_{1j}(t)\mathrm{d}a + \int_0^{+\infty}\sum_{j=1}^n \beta_{ij}(a)S_i^0(a)U_{1j}(t)\mathrm{d}a.
\end{aligned} \tag{5.8}$$

Note that $G\left(S_i(t,0)/S_i^0(a)\right) = 0$, $i \in \mathcal{N}$ since $S_i^0(0) = S_i(t,0) = \Lambda_i$ and $G(1) = 0$.

The derivative of $L_{2i}(t)$ along the solution trajectory of system (1.2) is calculated as follows.

$$\begin{aligned}
L_{2i}'(t) &= \int_0^{+\infty} \zeta_i(a)\frac{\partial U_{2i}(t,a)}{\partial t}\mathrm{d}a = -\int_0^{+\infty} \zeta_i(a)\frac{\partial U_{2i}(t,a)}{\partial a}\mathrm{d}a - \int_0^{+\infty} \zeta_i(a)\alpha_i(a)U_{2i}(t,a)\mathrm{d}a \\
&= -\zeta_i(a)U_{2i}(t,a)|_{a=0}^{a=+\infty} + \int_0^{+\infty} U_{2i}(t,a)\frac{\mathrm{d}\zeta_i(a)}{\mathrm{d}a}\mathrm{d}a - \int_0^{+\infty} \zeta_i(a)\alpha_i(a)U_{2i}(t,a)\mathrm{d}a \\
&= \zeta_i(0)U_{2i}(t,0) + \int_0^{+\infty} U_{2i}(t,a)\big(\zeta_i(a)\alpha_i(a) - \gamma_i(a)\big)\mathrm{d}a - \int_0^{+\infty} \zeta_i(a)\alpha_i(a)U_{2i}(t,a)\mathrm{d}a \\
&= \zeta_i(0)U_{2i}(t,0) - \int_0^{+\infty} U_{2i}(t,a)\gamma_i(a)\mathrm{d}a = \theta_i p_i U_{1i}(t) - \int_0^{+\infty} U_{2i}(t,a)\gamma_i(a)\mathrm{d}a, \quad i \in \mathcal{N}.
\end{aligned} \tag{5.9}$$

From (5.8)-(5.9) and the second equation of (1.2), the derivative of the Lyapunov function $V_0(\mathbf{x}(t))$ is calculated as

$$\begin{aligned}
V_0'(\mathbf{x}(t)) &= \sum_{i=1}^n c_i\left[-S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\Bigg|^{a=+\infty} - \int_0^{+\infty}\mu_i S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\mathrm{d}a\right. \\
&\quad \left. + \int_0^{+\infty}\sum_{j=1}^n \beta_{ij}(a)S_i^0(a)U_{1j}(t)\mathrm{d}a - \left[\mu_i + \delta_{1i} + p_i(1-\theta_i)\right]U_{1i}(t)\right] \\
&\leq \sum_{i=1}^n c_i\left[\int_0^{+\infty}\sum_{j=1}^n \beta_{ij}(a)S_i^0(a)U_{1j}(t)\mathrm{d}a - [\mu_i + \delta_{1i} + p_i(1-\theta_i)]U_{1i}(t)\right] \\
&= \sum_{i,j=1}^n \omega_i\left[\frac{\int_0^{+\infty}\beta_{ij}(a)S_i^0(a)U_{1j}(t)\mathrm{d}a}{\mu_i + \delta_{1i} + p_i(1-\theta_i)} - U_{1i}(t)\right] = (\omega_1, \omega_2, \cdots, \omega_n)\left(M_0\mathbf{U}_1(t) - \mathbf{U}_1(t)\right) \\
&= (\rho(M_0) - 1)(\omega_1, \omega_2, \cdots, \omega_n)\mathbf{U}_1(t) = (\Re_0 - 1)(\omega_1, \omega_2, \cdots, \omega_n)\mathbf{U}_1(t).
\end{aligned} \tag{5.10}$$

Therefore, it follows from $\Re_0 \le 1$ that $V_0'(\mathbf{x}(t)) \le 0$ holds for all $t > 0$.

To apply the invariance principle in [26, Theorem 4.2 in Chapter IV], we use the following notation.

$$\gamma(\mathbf{x}_0) := \cup_{t\ge 0}\{\Phi(t)\mathbf{x}_0\} = \cup_{t\ge 0}\{\mathbf{x}(t)\}, \quad \mathcal{M}_1 := \left\{\mathbf{x}\in C : V_0'(\mathbf{x}) = 0\right\}, \quad \mathcal{M} : \text{the largest invariant subset of } \mathcal{M}_1.$$

By Lemma 4.3 and Proposition 4.1, we see that $\gamma(\mathbf{x}_0) \subset C$ and $\gamma(\mathbf{x}_0)$ is precompact. It is obvious from the first equality in (5.10) that if $\mathbf{x} = \tilde{E}^0$, then $V_0'(\mathbf{x}) = 0$. In contrast, if $V_0'(\mathbf{x}) = 0$, then it follows from the first equality in (5.10) that

$$0 = \sum_{i=1}^n c_i\left[-S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\Bigg|^{a=+\infty} - \int_0^{+\infty}\mu_i S_i^0(a)G\left(\frac{S_i(t,a)}{S_i^0(a)}\right)\mathrm{d}a\right] + (\Re_0 - 1)(\omega_1,\omega_2,\cdots,\omega_n)\mathbf{U}_1(t). \qquad (5.11)$$

From the second term in the right-hand side of (5.11), we have that $S_i \equiv S_i^0$ for all $i \in \mathcal{N}$. If $U_{1i}(t) > 0$ for some $t > 0$ and $i \in \mathcal{N}$, then it follows from the first equation in (1.2) that $S_i \not\equiv S_i^0$, which is a contradiction. Hence, $U_{1i} \equiv 0$ for all $i \in \mathcal{N}$. Then, we see from the third equation in (1.2) that the largest invariant subset $\mathcal{M}$ of set $\mathcal{M}_1$ is the singleton $\{\tilde{E}^0\} \subset C$. By the invariance principle in [26, Theorem 4.2 in Chapter IV], we see that the drug-free equilibrium $\tilde{E}^0$ is globally attractive in C. By Proposition 5.1, it is globally asymptotically stable. This completes the proof. □

6. Persistence of the heroin users without treatment

In this section, we prove the uniform persistence of the heroin users without treatment for $\Re_0 > 1$, which is needed to guarantee the boundedness of the Lyapunov function in Section 7. Let us consider the following distance function $\rho : \mathbb{R}^n \to \mathbb{R}_+$: $\rho(\varphi) := \max(|\varphi_1|, |\varphi_2|, \cdots, |\varphi_n|)$, $\varphi = (\varphi_1,\varphi_2,\cdots,\varphi_n)^T \in \mathbb{R}^n$. We first prove the following lemma on the uniform weak ρ-persistence of the heroin users without treatment.

Lemma 6.1. *Suppose that $\Re_0 > 1$. There exists a positive constant $\epsilon_0 > 0$ such that if $\mathbf{x}_0 \in C_0$, then*

$$\limsup_{t\to+\infty}\rho(\mathbf{U}_1(t)) \ge \epsilon_0. \qquad (6.1)$$

Proof. Since $\Re_0 = r(M^0) > 1$, it follows from the continuity and the Perron-Frobenius theorem ([21]) that there exist sufficiently small $\epsilon_0 > 0$, small $\lambda_0 > 0$ and large $T_0 > 0$ such that $r(\hat{M}) > 1$, where

$$\hat{M} := \left(\frac{\int_0^{T_0}\beta_{ij}(a)S_i^0(a)\mathrm{e}^{-\epsilon_0\int_0^a\sum_{j=1}^n\beta_{ij}(\sigma)\mathrm{d}\sigma}\mathrm{d}a}{\lambda_0 + \mu_i + \delta_{1i} + \left(1 - \int_0^{+\infty}\gamma_i(a)\varrho_i(a)\mathrm{e}^{-\lambda_0 a}\mathrm{d}a\right)p_i}\right)_{i,j\in\mathcal{N}}.$$

For such $\epsilon_0 > 0$, suppose that (6.1) does not hold. Then, without loss of generality, we can assume that $T_0 > 0$ is large so that $U_{1i}(t) < \epsilon_0$ for all $t \ge T_0$ and $i \in \mathcal{N}$. From the first equation in (1.2), we have, for all $t \ge T_0$ and $a \in (0,t)$,

$$S_i(t,a) \ge \Lambda_i\mathrm{e}^{-\epsilon_0\int_0^a\sum_{j=1}^n\beta_{ij}(\sigma)\mathrm{d}\sigma - \mu_i a} = S_i^0(a)\mathrm{e}^{-\epsilon_0\int_0^a\sum_{j=1}^n\beta_{ij}(\sigma)\mathrm{d}\sigma}, \quad i \in \mathcal{N}. \qquad (6.2)$$

From the second equation in (1.2), we then have, for all $t \ge T_0$ and $i \in \mathcal{N}$,

$$\begin{aligned}\frac{\mathrm{d}U_{1i}(t)}{\mathrm{d}t} &\ge \sum_{j=1}^n\int_0^t\beta_{ij}(a)S_i(t,a)\mathrm{d}aU_{1j}(t) - (\mu_i + \delta_{1i} + p_i)U_{1i}(t) + \int_0^t\gamma_i(a)U_{2i}(t,a)\mathrm{d}a \\ &\ge \sum_{j=1}^n\int_0^{T_0}\beta_{ij}(a)S_i^0(a)\mathrm{e}^{-\epsilon_0\int_0^a\sum_{j=1}^n\beta_{ij}(\sigma)\mathrm{d}\sigma}\mathrm{d}aU_{1j}(t) - (\mu_i + \delta_{1i} + p_i)U_{1i}(t) + \int_0^t\gamma_i(a)p_iU_{1i}(t-a)\varrho_i(a)\mathrm{d}a. \qquad (6.3)\end{aligned}$$

By taking $\Phi(T_0)\mathbf{x}_0 \in C_0$ as a new initial condition, we can assume without loss of generality that the inequality (6.3) holds for all $t \ge 0$ and $i \in \mathcal{N}$. Multiplying $\mathrm{e}^{-\lambda_0 t}$ by both sides of (6.3) and integrating from 0 to $+\infty$, we have

$$\begin{aligned}\int_0^{+\infty}\mathrm{e}^{-\lambda_0 t}\frac{\mathrm{d}U_{1i}(t)}{\mathrm{d}t}\mathrm{d}t \ge& \sum_{j=1}^n\int_0^{T_0}\beta_{ij}(a)S_i^0(a)\mathrm{e}^{-\epsilon_0\int_0^a\sum_{j=1}^n\beta_{ij}(\sigma)\mathrm{d}\sigma}\mathrm{d}a\,\mathcal{L}[U_{1j}](\lambda_0) \\ &- (\mu_i + \delta_{1i} + p_i)\mathcal{L}[U_{1i}](\lambda_0) + p_i\int_0^{+\infty}\gamma_i(a)\varrho_i(a)\mathrm{e}^{-\lambda_0 a}\mathrm{d}a\,\mathcal{L}[U_{1i}](\lambda_0), \quad i \in \mathcal{N}, \qquad (6.4)\end{aligned}$$

where $\mathcal{L}[U_{1i}](\lambda_0) := \int_0^{+\infty} e^{-\lambda_0 t} U_{1i}(t)dt$, $i \in \mathcal{N}$ denotes the Laplace transform of U_{1i}, $i \in \mathcal{N}$. Note that $\mathcal{L}[U_{1i}](\lambda_0) \in (0, +\infty)$ for all $i \in \mathcal{N}$ by virtue of Lemma 4.3. By applying integration by parts to (6.4), we have, for all $i \in \mathcal{N}$,

$$\left\{\lambda_0 + \mu_i + \delta_{1i} + \left(1 - \int_0^{+\infty} \gamma_i(a)\varrho_i(a)e^{-\lambda_0 a}da\right)p_i\right\}\mathcal{L}[U_{1i}](\lambda_0) \geq \sum_{j=1}^{n} \int_0^{T_0} \beta_{ij}(a)S_i^0(a)e^{-\epsilon_0 \int_0^a \sum_{j=1}^n \beta_{ij}(\sigma)d\sigma}da\, \mathcal{L}[U_{1j}](\lambda_0).$$

Hence, we obtain the following inequality in the vector-matrix form: $\mathcal{L}[\mathbf{U}_1](\lambda_0) \geq \hat{M}\mathcal{L}[\mathbf{U}_1](\lambda_0)$, where $\mathcal{L}[\mathbf{U}_1](\lambda_0) := (\mathcal{L}[U_{11}](\lambda_0), \cdots, \mathcal{L}[U_{1n}](\lambda_0))^T$. Let $\hat{\mathbf{w}}$ be the left positive Perron-Frobenius eigenvector of matrix $\hat{M}$, associated with $r(\hat{M}) > 1$. We then have $\hat{\mathbf{w}}\mathcal{L}[\mathbf{U}_1](\lambda_0) \geq \hat{\mathbf{w}}\hat{M}\mathcal{L}[\mathbf{U}_1](\lambda_0) = r(\hat{M})\hat{\mathbf{w}}\mathcal{L}[\mathbf{U}_1](\lambda_0) > \hat{\mathbf{w}}\mathcal{L}[\mathbf{U}_1](\lambda_0)$, which is a contradiction. This completes the proof. □

Using Lemma 6.1, we next prove the uniform strong ρ-persistence of the heroin users without treatment for $\mathfrak{R}_0 > 1$.

Proposition 6.1. *Suppose that $\mathfrak{R}_0 > 1$. There exists a positive constant $\epsilon_1 \in (0, \epsilon_0)$ such that if $\mathbf{x}_0 \in C_0$, then*

$$\liminf_{t\to+\infty} \rho(\mathbf{U}_1(t)) \geq \epsilon_1. \tag{6.5}$$

Proof. Suppose that (6.5) does not hold. By Lemma 6.1, there exist increasing sequences $\{t_n\}_{n=1}^{+\infty}$ and $\{s_n\}_{n=1}^{+\infty}$ such that, for all $n \in \mathbb{N}$,

$$t_n < s_n, \quad \rho(\mathbf{U}_1(t_n)) = \rho(\mathbf{U}_1(s_n)) = \epsilon_0 \text{ and } \rho(\mathbf{U}_1(t)) < \epsilon_0 \text{ for all } t \in (t_n, s_n). \tag{6.6}$$

From the second equation in (1.2), we have $U'_{1i}(t) \geq -(\mu_i + \delta_{1i} + p_i)U_{1i}(t) \geq -dU_{1i}(t)$ for all $t > 0$ and $i \in \mathcal{N}$, where $d := \max_{i\in\mathcal{N}}\{\mu_i + \delta_{1i} + p_i\}$. Hence, we have

$$U_{1i}(t) \geq U_{1i}(t_n)e^{-d(t-t_n)}, \quad t \in (t_n, s_n),\ n \in \mathbb{N},\ i \in \mathcal{N}. \tag{6.7}$$

If there exists a positive constant $T_1 > 0$ such that $\sup_{n\in\mathbb{N}}(s_n - t_n) \leq T_1$, then we have from (6.6) and (6.7) that $\liminf_{t\to+\infty} \rho(\mathbf{U}_1(t)) \geq \epsilon_0 e^{-dT_1}$. Hence, (6.5) holds for $\epsilon_1 = \epsilon_0 e^{-dT_1}$. If $\sup_{n\in\mathbb{N}}(s_n - t_n) = +\infty$, then we can take subsequences $\{(\tilde{t}_n, \tilde{s}_n)\}_{n=1}^{+\infty} \subset \{(t_n, s_n)\}_{n=1}^{+\infty}$ such that $\tilde{s}_n - \tilde{t}_n > \tilde{T}_n$ for all $n \in \mathbb{N}$, where $\{\tilde{T}_n\}_{n=1}^{+\infty}$ is an increasing sequence such that $\tilde{T}_n \to +\infty$ as $n \to +\infty$. For sufficiently large $n \in \mathbb{N}$, we have $\tilde{t}_n > T_0$, where $T_0 > 0$ is as in the proof of Lemma 6.1. For such $n \in \mathbb{N}$, it follows from the last inequality in (6.6) that the inequality (6.2) holds for all $t \in (\tilde{t}_n, \tilde{s}_n)$, $a \in (0, t)$ and $i \in \mathcal{N}$. Hence, as in the proof of Lemma 6.1, the inequality (6.3) holds for all $t \in (\tilde{t}_n, \tilde{s}_n)$ and $i \in \mathcal{N}$. By taking $\Phi(\tilde{t}_n)\mathbf{x}_0 \in C_0$ as a new initial condition, we can assume without loss of generality that the inequality (6.3) holds for all $t \in (0, \tilde{T}_n) \subset (0, \tilde{s}_n - \tilde{t}_n)$ and $i \in \mathcal{N}$. Let $\lambda_0 > 0$ be as in the proof of Lemma 6.1. Multiplying $e^{-\lambda_0 t}$ by both sides of (6.3) and integrating from 0 to $\tilde{T}_n$, we have

$$\begin{aligned}\int_0^{\tilde{T}_n} e^{-\lambda_0 t}\frac{dU_{1i}(t)}{dt}dt \geq &\sum_{j=1}^{n}\int_0^{T_0} \beta_{ij}(a)S_i^0(a)e^{-\epsilon_0 \int_0^a \sum_{j=1}^n \beta_{ij}(\sigma)d\sigma}da \int_0^{\tilde{T}_n} e^{-\lambda_0 t}U_{1i}(t)dt \\ &- (\mu_i + \delta_{1i} + p_i)\int_0^{\tilde{T}_n} e^{-\lambda_0 t}U_{1i}(t)dt + p_i\int_0^{\tilde{T}_n} e^{-\lambda_0 t}\int_0^t \gamma_i(a)\varrho_i(a)U_{1i}(t-a)dadt, \quad i \in \mathcal{N}.\end{aligned} \tag{6.8}$$

Taking $n \to +\infty$ in (6.8), we obtain (6.4). Hence, as in the proof of Lemma 6.1, we can show a contradiction. This completes the proof. □

Using Proposition 6.1, we prove the uniform strong persistence of the heroin users without treatment for $\mathfrak{R}_0 > 1$.

Theorem 6.1. *Suppose that $\mathfrak{R}_0 > 1$. There exists a positive constant $\epsilon_2 > 0$ such that if $\mathbf{x}_0 \in C_0$, then*

$$\liminf_{t\to+\infty} U_{1i}(t) \geq \epsilon_2 \quad \text{for all } i \in \mathcal{N}. \tag{6.9}$$

Proof. From the first equation in (1.2) and Lemma 4.3, we have, for all $t > 0$ and $a \in (0, t)$,

$$S_i(t,a) \geq \Lambda_i e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma - \mu_i a} = S_i^0(a) e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma}, \quad i \in \mathcal{N}. \tag{6.10}$$

From the second equation in (1.2), we then have, for all $t > 0$,

$$\begin{aligned}
\frac{dU_{1i}(t)}{dt} &\geq \sum_{j=1}^n \int_0^t \beta_{ij}(a) S_i(t,a) da U_{1j}(t) - (\mu_i + \delta_{1i} + p_i) U_{1i}(t) \\
&\geq \sum_{j=1}^n \int_0^t \beta_{ij}(a) S_i^0(a) e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma} da U_{1j}(t) - (\mu_i + \delta_{1i} + p_i) U_{1i}(t), \quad i \in \mathcal{N}.
\end{aligned}$$

Then, by the variation of constants formula, we have

$$\begin{aligned}
U_{1i}(t) &\geq \int_0^t e^{-(\mu_i+\delta_{1i}+p_i)(t-u)} \sum_{j=1}^n \int_0^u \beta_{ij}(a) S_i^0(a) e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma} da U_{1j}(u) du \\
&= \int_0^t e^{-(\mu_i+\delta_{1i}+p_i)u} \sum_{j=1}^n \int_0^{t-u} \beta_{ij}(a) S_i^0(a) e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma} da U_{1j}(t-u) du, \quad i \in \mathcal{N}.
\end{aligned} \tag{6.11}$$

By Proposition 6.1, there exists a $j^* \in \mathcal{N}$ such that $\liminf_{t\to+\infty} \rho(\mathbf{U}_1(t)) = \liminf_{t\to+\infty} U_{1j^*}(t) \geq \epsilon_1$. Taking $t \to +\infty$ in both sides of (6.11), we have

$$\begin{aligned}
\liminf_{t\to+\infty} U_{1i}(t) &\geq \int_0^{+\infty} e^{-(\mu_i+\delta_{1i}+p_i)u} \int_0^{+\infty} \beta_{ij^*}(a) S_i^0(a) e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma} da du \liminf_{t\to+\infty} U_{1j^*}(t) \\
&\geq \int_0^{+\infty} e^{-(\mu_i+\delta_{1i}+p_i)u} \int_0^{+\infty} \beta_{ij^*}(a) S_i^0(a) e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma} da du\, \epsilon_1 \ =: \ \epsilon_{2,i}, \quad i \in \mathcal{N}.
\end{aligned}$$

Note that $\epsilon_{2,i} > 0$ for some $i \neq j^*$ by virtue of Assumption 1.1. Let $j^{**} \in \mathcal{N}$, $j^{**} \neq j^*$ be such that $\epsilon_{2,j^{**}} > 0$. Similar to the above inequality, we have

$$\liminf_{t\to+\infty} U_{1i}(t) \geq \int_0^{+\infty} e^{-(\mu_i+\delta_{1i}+p_i)u} \int_0^{+\infty} \beta_{ij^{**}}(a) S_i^0(a) e^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)d\sigma} da du\, \epsilon_{2,j^{**}} \ =: \ \tilde{\epsilon}_{2,i}, \quad i \in \mathcal{N}.$$

Note that $\tilde{\epsilon}_{2,i} > 0$ for some $i \neq j^{**}$ from Assumption 1.1. By repeating this argument, we see from the irreducibility of matrix $\left(\int_0^{+\infty} \beta_{ij}(a)da\right)_{i,j\in\mathcal{N}}$ that there exists an $\epsilon_2 > 0$ such that (6.9) holds. This completes the proof. □

7. Global attractivity of the drug-endemic equilibrium

In this section, we prove the global attractivity of the drug-endemic equilibrium $\tilde{E}^* \in C_0$ when $\mathfrak{R}_0 > 1$. By Theorem 2.1, the drug-endemic equilibrium $\tilde{E}^*$ exists when $\mathfrak{R}_0 > 1$. To prove the global attractivity of it, we will construct the Lyapunov function that includes the following functions. For all $t > 0$ and $i \in \mathcal{N}$, we define

$$W_{1i}(t) := \int_0^{+\infty} S_i^*(a) G\left(\frac{S_i(t,a)}{S_i^*(a)}\right) da, \ W_{2i}(t) := U_{1i}^* G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right), \ W_{3i}(t) := \int_0^{+\infty} \zeta_i(a) U_{2i}^*(a) G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right) da, \tag{7.1}$$

where $G(\cdot)$ is defined as in Section 5, and $\zeta_i(\cdot)$, $i \in \mathcal{N}$ is defined by (5.7). Let us define the following set.

$$\begin{aligned}
C_1 := \Bigg\{ \mathbf{x} = (0_{\mathbb{R}^n}, \psi_1, \varphi, 0_{\mathbb{R}^n}, \psi_2)^{\mathrm{T}} \in C : \ &\int_0^{+\infty} S_i^*(a) G\left(\frac{\psi_{1,i}(a)}{S_i^*(a)}\right) da, \ U_{1i}^* G\left(\frac{\varphi_i}{U_{1i}^*}\right) \text{ and } \int_0^{+\infty} \zeta_i(a) U_{2i}^*(a) G\left(\frac{\psi_{2,i}(a)}{U_{2i}^*(a)}\right) da \\
&\text{are finite for all } i \in \mathcal{N} \Bigg\},
\end{aligned}$$

which exists only if $\mathfrak{R}_0 > 1$. We prove the following lemma.

Lemma 7.1. *Suppose that $\Re_0 > 1$. C_1 attracts all solutions $\mathbf{x}(t) = \Phi(t)\mathbf{x}_0$ with $\mathbf{x}_0 \in C_0$.*

Proof. By Theorem 6.1, there exist a sufficiently large $\tau_0 > 0$ and small $\epsilon_3 (< \epsilon_2)$ such that $U_{1i}(t) \geq \epsilon_3$ for all $t \geq \tau_0$ and $i \in \mathcal{N}$. Hence, it follows from Lemma 4.3 and the definition of $G(\cdot)$ that

$$U_{1i}^* G\left(U_{1i}(t)/U_{1i}^*\right) \leq U_{1i}^* \max\left(G\left(\epsilon_3/U_{1i}^*\right), G\left((\Lambda_i/\mu_i)/U_{1i}^*\right)\right) < +\infty \tag{7.2}$$

for all $t \geq \tau_0$ and $i \in \mathcal{N}$. By (4.7) and (6.10), we have, for all $t > 0$ and $a \in (0, t)$,

$$S_i(t,a) \geq S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}, \quad U_{2i}(t,a) = p_i U_{1i}(t-a)\mathrm{e}^{-\int_0^a(\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}, \quad i \in \mathcal{N}. \tag{7.3}$$

Let $\tau_1 > 0$ be an arbitrary large constant and $\tau_2 = \tau_1 + \tau_0$. Then, from (7.3), the following inequalities hold for all $t > \tau_2$ and $a \in (0, \tau_1)$: $S_i(t,a) \geq S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n(\Lambda_j/\mu_j)\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}$, $U_{2i}(t,a) \geq p_i\epsilon_3\mathrm{e}^{-\int_0^a(\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}$, $i \in \mathcal{N}$. Hence, we have, for all $t > \tau_2$ and $i \in \mathcal{N}$,

$$\begin{aligned}
&\int_0^{\tau_1} S_i^*(a) G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\mathrm{d}a \leq \int_0^{\tau_1} S_i^*(a)\max\left(G\left(\frac{S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}}{S_i^*(a)}\right), G\left(\frac{S_i^0(a)}{S_i^*(a)}\right)\right)\mathrm{d}a \\
&= \int_0^{\tau_1} S_i^*(a)\max\left(G\left(\mathrm{e}^{-\sum_{j=1}^n\left(\frac{\Lambda_j}{\mu_j}-U_{1j}^*\right)\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}\right), G\left(\mathrm{e}^{\sum_{j=1}^n U_{1j}^*\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma}\right)\right)\mathrm{d}a \\
&\leq \int_0^{\tau_1} \max\left(S_i^0(a)\mathrm{e}^{-\sum_{j=1}^n \frac{\Lambda_j}{\mu_j}\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma} - S_i^*(a) + S_i^*(a)\sum_{j=1}^n\left(\frac{\Lambda_j}{\mu_j} - U_{1j}^*\right)\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma,\ S_i^0(a) - S_i^*(a) - S_i^*(a)\sum_{j=1}^n U_{1j}^*\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma\right)\mathrm{d}a \\
&\leq \int_0^{\tau_1}\left(S_i^0(a) + S_i^*(a) + S_i^*(a)\sum_{j=1}^n \kappa_j\int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma\right)\mathrm{d}a \leq \int_0^{\tau_1} S_i^0(a)\left(2 + \sum_{j=1}^n \kappa_j \int_0^a \beta_{ij}(\sigma)\mathrm{d}\sigma\right)\mathrm{d}a \\
&\leq \int_0^{+\infty} S_i^0(a)\mathrm{d}a\left(2 + \sum_{j=1}^n \kappa_j\int_0^{+\infty}\beta_{ij}(\sigma)\mathrm{d}\sigma\right) < +\infty,
\end{aligned}$$

where $\kappa_j := \Lambda_j/\mu_j - U_{1j}^* > 0$, $j \in \mathcal{N}$. Since τ_1 is arbitrary large, we have

$$\lim_{t\to+\infty}\int_0^{+\infty} S_i^*(a)G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\mathrm{d}a \leq \int_0^{+\infty} S_i^0(a)\mathrm{d}a\left(2 + \sum_{j=1}^n \kappa_j\int_0^{+\infty}\beta_{ij}(\sigma)\mathrm{d}\sigma\right) < +\infty, \quad i \in \mathcal{N}. \tag{7.4}$$

In addition, we have, for all $t > \tau_2$, $a \in (0, \tau_1)$ and $i \in \mathcal{N}$,

$$\frac{\epsilon_3}{U_{1i}^*} \leq \frac{p_i\epsilon_3\mathrm{e}^{-\int_0^a(\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}}{p_iU_{1i}^*\mathrm{e}^{-\int_0^a(\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}} \leq \frac{U_{2i}(t,a)}{U_{2i}^*(a)} \leq \frac{p_i\frac{\Lambda_i}{\mu_i}\mathrm{e}^{-\int_0^a(\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}}{p_iU_{1i}^*\mathrm{e}^{-\int_0^a(\mu_i+\delta_{2i}+\gamma_i(\sigma))\mathrm{d}\sigma}} \leq \frac{\Lambda_i}{\mu_iU_{1i}^*}.$$

Hence, similar to (7.4), we have

$$\lim_{t\to+\infty}\int_0^{+\infty}\zeta_i(a)U_{2i}^*(a)G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right)\mathrm{d}a \leq \int_0^{+\infty}\zeta_i(a)U_{2i}^*(a)\mathrm{d}a\max\left(G\left(\frac{\epsilon_3}{U_{1i}^*}\right), G\left(\frac{\Lambda_i}{\mu_iU_{1i}^*}\right)\right) < +\infty, \quad i \in \mathcal{N}. \tag{7.5}$$

From (7.2), (7.4) and (7.5), the assertion holds. This completes the proof. □

By virtue of Lemma 7.1, under the assumptions that $\Re_0 > 1$ and $\mathbf{x}_0 \in C_0$, we can restrict our attention on the solution in C_1, in which the Lyapunov function below is well constructed. To apply the graph-theoretic approach as in [16], we define the following Laplacian matrix.

$$\mathbf{B} := \begin{pmatrix} \Sigma_{l\neq1}\bar{\beta}_{1l} & -\bar{\beta}_{21} & \cdots & -\bar{\beta}_{n1} \\ -\bar{\beta}_{12} & \Sigma_{l\neq2}\bar{\beta}_{2l} & \cdots & -\bar{\beta}_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ -\bar{\beta}_{1n} & -\bar{\beta}_{2n} & \cdots & \Sigma_{l\neq n}\bar{\beta}_{nl} \end{pmatrix}, \quad \bar{\beta}_{ij} := \int_0^{+\infty}\beta_{ij}(a)S_i^*(a)\mathrm{d}a\ U_{1j}^*, \quad i, j \in \mathcal{N}.$$

We see that $\mathbf{B}$ is irreducible under Assumption 1.1. Hence, as in [16, Section 2], we see that for the cofactor v_i, $i \in \mathcal{N}$ of the (i,i) entry of $\mathbf{B}$, it follows that $\mathbf{B}\mathbf{v} = 0_{\mathbb{R}^n}$, where $\mathbf{v} = (v_1, v_2, \cdots, v_n)^{\mathrm{T}}$. By using this vector $\mathbf{v}$, we define the following Lyapunov function: $V_1(\mathbf{x}(t)) = \sum_{i=1}^n v_i (W_{1i}(t) + W_{2i}(t) + W_{3i}(t))$, where W_{1i}, W_{2i} and W_{3i}, $i \in \mathcal{N}$ are defined by (7.1). Using this Lyapunov function, we prove the following theorem on the global asymptotic stability of the drug-endemic equilibrium $\tilde{E}^*$ in C_0 when $\Re_0 > 1$.

Theorem 7.1. *Suppose that $\Re_0 > 1$. The drug-endemic equilibrium $\tilde{E}^*$ of* (1.2) *is globally attractive in C_0.*

Proof. By Lemma 7.1, in the asymptotic analysis of system (1.2), we can restrict our attention on the solution in C_1, in which $V_1(\mathbf{x}(t))$ is finite. We first calculate the derivative of $W_{1i}(t)$ along the solution trajectory of system (1.2).

$$W_{1i}'(t) = \int_0^{+\infty} S_i^*(a)\left(1 - \frac{S_i^*(a)}{S_i(t,a)}\right)\frac{1}{S_i^*(a)}\frac{\partial S_i(t,a)}{\partial t}\mathrm{d}a = -\int_0^{+\infty} S_i^*(a)\left(\frac{S_i(t,a)}{S_i^*(a)} - 1\right)\left(\frac{\partial_a S_i(t,a)}{S_i(t,a)} + \mu_i + \sum_{j=1}^n \beta_{ij}(a)U_{1j}(t)\right)\mathrm{d}a, \quad i \in \mathcal{N},$$

where ∂_a denotes $\partial/\partial a$. Recalling that $(S_i^*)'(a) = -\left(\sum_{j=1}^n \beta_{ij}(a)U_{1j}^* + \mu_i\right)S_i^*(a)$, $i \in \mathcal{N}$, it follows that

$$\frac{\partial}{\partial a}G\left(\frac{S_i(t,a)}{S_i^*(a)}\right) = \left(\frac{S_i(t,a)}{S_i^*(a)} - 1\right)\left(\frac{\partial_a S_i(t,a)}{S_i(t,a)} + \mu_i + \sum_{j=1}^n \beta_{ij}(a)U_{1j}^*\right), \quad i \in \mathcal{N}.$$

Hence, by using the integration by parts, we have

$$\begin{aligned}
W_{1i}'(t) &= -\int_0^{+\infty} S_i^*(a)\frac{\partial}{\partial a}G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\mathrm{d}a - \int_0^{+\infty} S_i^*(a)\left(\frac{S_i(t,a)}{S_i^*(a)} - 1\right)\sum_{j=1}^n \beta_{ij}(a)\left(U_{1j}(t) - U_{1j}^*\right)\mathrm{d}a \\
&= -S_i^*(a)G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\Bigg|_{a=0}^{a=+\infty} + \int_0^{+\infty} G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\frac{\mathrm{d}}{\mathrm{d}a}S_i^*(a)\mathrm{d}a \\
&\quad - \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}a\left(U_{1j}(t) - U_{1j}^*\right) + \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i^*(a)\mathrm{d}a\left(U_{1j}(t) - U_{1j}^*\right) \\
&= -S_i^*(a)G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\Bigg|^{a=+\infty} - \int_0^{+\infty} G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\left(\sum_{j=1}^n \beta_{ij}(a)U_{1j}^* + \mu_i\right)S_i^*(a)\mathrm{d}a \\
&\quad - \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}a\left(U_{1j}(t) - U_{1j}^*\right) + \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i^*(a)\mathrm{d}a\left(U_{1j}(t) - U_{1j}^*\right), \quad i \in \mathcal{N}.
\end{aligned} \tag{7.6}$$

Note that $G\left(S_i(t,0)/S_i^*(0)\right) = 0$, $i \in \mathcal{N}$ since $S_i^*(0) = S_i(t,0) = \Lambda_i$ and $G(1) = 0$.

We next calculate the derivative of $W_{2i}(t)$ along the solution trajectory of system (1.2). By using the second equation of (2.2), we have

$$\begin{aligned}
W_{2i}'(t) &= \left(1 - \frac{U_{1i}^*}{U_{1i}(t)}\right)\left(\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}aU_{1j}(t) - (\mu_i + \delta_{1i} + p_i)U_{1i}(t) + \int_0^{+\infty} \gamma_i(a)U_{2i}(t,a)\mathrm{d}a\right) \\
&= \left(1 - \frac{U_{1i}^*}{U_{1i}(t)}\right)\left(\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}aU_{1j}(t) + \int_0^{+\infty} \gamma_i(a)U_{2i}(t,a)\mathrm{d}a\right) \\
&\quad + \left(1 - \frac{U_{1i}(t)}{U_{1i}^*}\right)\left(\sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i^*(a)\mathrm{d}aU_{1j}^* + \int_0^{+\infty} \gamma_i(a)U_{2i}^*(a)\mathrm{d}a\right) \\
&= \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}a\left(U_{1j}(t) - U_{1j}(t)\frac{U_{1i}^*}{U_{1i}(t)}\right) + \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i^*(a)\mathrm{d}a\left(U_{1j}^* - U_{1j}^*\frac{U_{1i}(t)}{U_{1i}^*}\right) \\
&\quad + \int_0^{+\infty} \gamma_i(a)U_{2i}^*(a)\left(1 - \frac{U_{1i}(t)}{U_{1i}^*} + \frac{U_{2i}(t,a)}{U_{2i}^*(a)} - \frac{U_{1i}^*U_{2i}(t,a)}{U_{1i}(t)U_{2i}^*(a)}\right)\mathrm{d}a \\
&= \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i(t,a)\mathrm{d}a\left(U_{1j}(t) - U_{1j}(t)\frac{U_{1i}^*}{U_{1i}(t)}\right) + \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a)S_i^*(a)\mathrm{d}a\left(U_{1j}^* - U_{1j}^*\frac{U_{1i}(t)}{U_{1i}^*}\right) \\
&\quad + \int_0^{+\infty} \gamma_i(a)U_{2i}^*(a)\left[-G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) + G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right) - G\left(\frac{U_{1i}^*U_{2i}(t,a)}{U_{1i}(t)U_{2i}^*(a)}\right)\right]\mathrm{d}a, \quad i \in \mathcal{N}.
\end{aligned} \tag{7.7}$$

We then calculate the derivative of $W_{3i}(t)$ along the solution trajectory of system (1.2). For all $i \in \mathcal{N}$, we have

$$W_{3i}'(t) = \int_0^{+\infty} \zeta_i(a) U_{2i}^*(a) \left(1 - \frac{U_{2i}^*(a)}{U_{2i}(t,a)}\right) \frac{1}{U_{2i}^*(a)} \frac{\partial U_{2i}(t,a)}{\partial t} \mathrm{d}a = -\int_0^{+\infty} \zeta_i(a) U_{2i}^*(a) \left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)} - 1\right) \left(\frac{\partial_a U_{2i}(t,a)}{U_{2i}(t,a)} + \alpha_i(a)\right) \mathrm{d}a.$$

Recalling that $(U_{2i}^*)'(a) = -\alpha_i(a) U_{2i}^*(a)$, $i \in \mathcal{N}$, we have

$$\frac{\partial}{\partial a} G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right) = \left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)} - 1\right) \left(\frac{\partial_a U_{2i}(t,a)}{U_{2i}(t,a)} + \alpha_i(a)\right), \quad i \in \mathcal{N}.$$

Hence, using integration by parts, we have

$$\begin{aligned}
W_{3i}'(t) &= -\int_0^{+\infty} \zeta_i(a) U_{2i}^*(a) \frac{\partial}{\partial a} G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right) \mathrm{d}a = -\zeta_i(a) U_{2i}^*(a) G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right)\Bigg|_{a=0}^{a=+\infty} + \int_0^{+\infty} G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right) \frac{\partial}{\partial a}(\zeta_i(a) U_{2i}^*(a)) \mathrm{d}a \\
&= \zeta_i(0) U_{2i}^*(0) G\left(\frac{U_{2i}(t,0)}{U_{2i}^*(0)}\right) - \int_0^{+\infty} \gamma_i(a) U_{2i}^*(a) G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right) \mathrm{d}a = \theta_i p_i U_{1i}^* G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) - \int_0^{+\infty} \gamma_i(a) U_{2i}^*(a) G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right) \mathrm{d}a \\
&= \int_0^{+\infty} \gamma_i(a) U_{2i}^*(a) \left[G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) - G\left(\frac{U_{2i}(t,a)}{U_{2i}^*(a)}\right)\right] \mathrm{d}a, \quad i \in \mathcal{N}.
\end{aligned} \tag{7.8}$$

Note that $\zeta_i(0) = \theta_i$, $U_{2i}^*(0) = p_i U_{1i}^*$, $U_{2i}(t,0) = p_i U_{1i}(t)$ and hence, $G\left(U_{2i}(t,0)/U_{2i}^*(0)\right) = G\left(U_{1i}(t)/U_{1i}^*\right)$, $i \in \mathcal{N}$.

From (7.6)-(7.8), we can calculate the derivative of the Lyapunov function $V_1(\mathbf{x}(t))$ as follows.

$$\begin{aligned}
V_1'(\mathbf{x}(t)) =& \sum_{i=1}^n v_i \left(W_{1i}'(t) + W_{2i}'(t) + W_{3i}'(t)\right) \\
=& \sum_{i=1}^n v_i \Bigg[-S_i^*(a) G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\Bigg|^{a=+\infty} - \int_0^{+\infty} G\left(\frac{S_i(t,a)}{S_i^*(a)}\right) \left(\sum_{j=1}^n \beta_{ij}(a) U_{1j}^* + \mu_i\right) S_i^*(a) \mathrm{d}a \\
&+ \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a) S_i(t,a) \mathrm{d}a \left(U_{1j}^* - U_{1j}(t) \frac{U_{1i}^*}{U_{1i}(t)}\right) + \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a) S_i^*(a) \mathrm{d}a \left(U_{1j}(t) - U_{1j}^* \frac{U_{1i}(t)}{U_{1i}^*}\right) \\
&- \int_0^{+\infty} \gamma_i(a) U_{2i}^*(a) G\left(\frac{U_{1i}^* U_{2i}(t,a)}{U_{1i}(t) U_{2i}^*(a)}\right) \mathrm{d}a \Bigg] \\
\leq& \sum_{i=1}^n v_i \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a) S_i^*(a) U_{1j}^* \left[-G\left(\frac{S_i(t,a)}{S_i^*(a)}\right) + \frac{S_i(t,a)}{S_i^*(a)} - \frac{S_i(t,a) U_{1j}(t) U_{1i}^*}{S_i^*(a) U_{1j^*} U_{1i}(t)} + \frac{U_{1j}(t)}{U_{1j}^*} - \frac{U_{1i}(t)}{U_{1i}^*} \right] \mathrm{d}a \\
=& \sum_{i=1}^n v_i \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a) S_i^*(a) U_{1j}^* \left[-G\left(\frac{S_i(t,a)}{S_i^*(a)}\right) + G\left(\frac{S_i(t,a)}{S_i^*(a)}\right) - G\left(\frac{S_i(t,a) U_{1j}(t) U_{1i}^*}{S_i^*(a) U_{1j^*} U_{1i}(t)}\right) + G\left(\frac{U_{1j}(t)}{U_{1j}^*}\right) - G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) \right] \mathrm{d}a \\
\leq& \sum_{i=1}^n v_i \sum_{j=1}^n \int_0^{+\infty} \beta_{ij}(a) S_i^*(a) \mathrm{d}a U_{1j}^* \left[G\left(\frac{U_{1j}(t)}{U_{1j}^*}\right) - G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) \right] = \sum_{i=1}^n v_i \sum_{j=1}^n \tilde{\beta}_{ij} \left[G\left(\frac{U_{1j}(t)}{U_{1j}^*}\right) - G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) \right].
\end{aligned} \tag{7.9}$$

Since $\mathbf{B}\mathbf{v} = 0_{\mathbb{R}^n}$, we have $\sum_{j=1}^n v_i \tilde{\beta}_{ij} = \sum_{j=1}^n v_j \tilde{\beta}_{ji}$ for all $i \in \mathcal{N}$. Hence, from (7.9), we have

$$\begin{aligned}
V_1'(\mathbf{x}(t)) \leq& \sum_{i=1}^n \sum_{j=1}^n v_i \tilde{\beta}_{ij} G\left(\frac{U_{1j}(t)}{U_{1j}^*}\right) - \sum_{i=1}^n \sum_{j=1}^n v_i \tilde{\beta}_{ij} G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) = \sum_{i=1}^n \sum_{j=1}^n v_j \tilde{\beta}_{ji} G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) - \sum_{i=1}^n \sum_{j=1}^n v_i \tilde{\beta}_{ij} G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) \\
=& \sum_{i=1}^n G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) \sum_{j=1}^n v_j \tilde{\beta}_{ji} - \sum_{i=1}^n \sum_{j=1}^n v_i \tilde{\beta}_{ij} G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) = \sum_{i=1}^n G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) \sum_{j=1}^n v_i \tilde{\beta}_{ij} - \sum_{i=1}^n \sum_{j=1}^n v_i \tilde{\beta}_{ij} G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) \\
=& \sum_{i=1}^n \sum_{j=1}^n v_i \tilde{\beta}_{ij} G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) - \sum_{i=1}^n \sum_{j=1}^n v_i \tilde{\beta}_{ij} G\left(\frac{U_{1i}(t)}{U_{1i}^*}\right) = 0.
\end{aligned} \tag{7.10}$$

Thus, we see that $V_1'(\mathbf{x}(t)) \leq 0$ holds for all $t > 0$.

We define $\gamma(\mathbf{x}_0)$ as in the proof of Theorem 5.1, and

$$\tilde{\mathcal{M}}_1 := \{\mathbf{x} \in C_1 : V_1'(\mathbf{x}) = 0\}, \quad \tilde{\mathcal{M}}: \text{ the largest invariant subset of } \tilde{\mathcal{M}}_1.$$

By Proposition 4.1 and Lemma 7.1, we see that $\gamma(\mathbf{x}_0) \subset C_1$ and $\gamma(\mathbf{x}_0)$ is precompact. It is easy to see from the second equality in (7.9) that if $\mathbf{x} = \tilde{E}^*$, then $V_1'(\mathbf{x}) = 0$. In contrast, if $V_1'(\mathbf{x}) = 0$, then it follows from (7.9) and (7.10) that

$$\begin{aligned} 0 = \sum_{i=1}^{n} v_i \Bigg[&-S_i^*(a) G\left(\frac{S_i(t,a)}{S_i^*(a)}\right)\Bigg|^{a=+\infty} - \mu_i \int_0^{+\infty} G\left(\frac{S_i(t,a)}{S_i^*(a)}\right) S_i^*(a)\mathrm{d}a - \int_0^{+\infty} \gamma_i(a) U_{2i}^*(a) G\left(\frac{U_{1i}^* U_{2i}(t,a)}{U_{1i}(t) U_{2i}^*(a)}\right)\mathrm{d}a \\ &- \sum_{j=1}^{n} \int_0^{+\infty} \beta_{ij}(a) S_i^*(a) U_{1j}^* G\left(\frac{S_i(t,a) U_{1j}(t) U_{1i}^*}{S_i^*(a) U_{1j^*} U_{1i}(t)}\right)\mathrm{d}a \Bigg]. \end{aligned}$$

From the last three terms in this equality, we have $S_i(t,a) = S_i^*(a)$ and $U_{2i}(t,a)/U_{2i}^*(a) = U_{1i}(t)/U_{1i}^* = U_{1j}(t)/U_{1j}^* = c$ for all $t \geq 0$, $a \geq 0$ and $i, j \in \mathcal{N}$, where $c > 0$ is a constant. Substituting $S_i = S_i^*$ and $U_{1i} = cU_{1i}^*$, $i \in \mathcal{N}$ into the first equation in (1.2), we have

$$\frac{\mathrm{d}S_i^*(a)}{\mathrm{d}a} = -c \sum_{j=1}^{n} \beta_{ij}(a) S_i^* U_{1j}^* - \mu_i S_i^*(a), \quad i \in \mathcal{N}.$$

From the uniqueness of the drug-endemic equilibrium (see Theorem 2.2), we have $c = 1$. Hence, the largest invariant subset $\tilde{\mathcal{M}}$ of set $\tilde{\mathcal{M}}_1$ is the singleton $\{\tilde{E}^*\} \subset C_1$. By the invariance principle in [26, Theorem 4.2 in Chapter IV], we see that the drug-endemic equilibrium $\tilde{E}^*$ is globally attractive. This completes the proof. □

8. Numerical simulation

In this section, we perform numerical simulation to illustrate our theoretical results. We consider the case where $n = 2$, which is suitable for considering sexual heterogeneity, that is, $i = 1$ implies male and $i = 2$ implies female. Note that the purpose of this section is to confirm the threshold property of $\mathfrak{R}_0$, and the parameters below are determined only from the technical purpose.

Method: We will employ an implicit Euler method (see Appendix for detailed program code).

Parameters setting: For uniform random variable $X \in (0, 1)$, we determine, for all $i, j \in \{1, 2\}$,

$$\Lambda_i = 1 + X, \ \ \mu_i = 1 + X, \ \ p_i = 0.1(1 + X), \ \ \delta_{1i} = 0.2(1 + X), \ \ \delta_{2i} = 0.05(1 + X),$$

$$\gamma_i(a) = 5(1 + X) \ \text{ for all } \ a \geq 0, \ \ \beta_{ij}(a) = \kappa_{ij}\beta(a), \ \ \kappa_{ij} = 1 + X,$$

where $\beta(a) = 0.5$ for all $a < 3$, and $\beta(a) = 0$ for all $a \geq 3$.

Initial condition setting: We determine, for all $a \geq 0$ and $i \in \{1, 2\}$,

$$S_{i,0}(a) = \Lambda_i \mathrm{e}^{-\mu_i a} / \int_0^{+\infty} \Lambda_i \mathrm{e}^{-\mu_i a} da, \ \ U_{1i}(0) = 0, \ \ U_{2i,0}(a) = 0.01 \times S_{i,0}(a).$$

We can easily check that Assumption 5.1 is satisfied for this initial condition.

Example 1 We set $\Lambda_1 = 1.3664$, $\Lambda_2 = 1.7719$, $\mu_1 = 1.3692$, $\mu_2 = 1.2057$, $p_1 = 0.1685$, $p_2 = 0.1388$, $\delta_{11} = 0.3196$, $\delta_{12} = 0.3104$, $\delta_{21} = 0.0895$, $\delta_{22} = 0.0614$, $\gamma_1(a) \equiv 6.8383$, $\gamma_2(a) \equiv 8.2097$, $\kappa_{11} = 1.2060$, $\kappa_{12} = 1.0867$, $\kappa_{21} = 1.4845$, $\kappa_{22} = 1.1518$ and $\mathfrak{R}_0 \approx 0.9077 < 1$. By Theorem 5.1, we can expect that the drug-free equilibrium is globally asymptotically stable. In fact, in Figure B.1 (a), $U_{11}(t)$ and $U_{12}(t)$ converge to zero as time evolves.

Example 2 We set $\Lambda_1 = 1.9116$, $\Lambda_2 = 1.5846$, $\mu_1 = 1.6393$, $\mu_2 = 1.2851$, $p_1 = 0.1255$, $p_2 = 0.1828$, $\delta_{11} = 0.2177$, $\delta_{12} = 0.2382$, $\delta_{21} = 0.0919$, $\delta_{22} = 0.0721$, $\gamma_1(a) \equiv 7.9236$, $\gamma_2(a) \equiv 6.9671$, $\kappa_{11} = 1.9481$, $\kappa_{12} = 1.0610$, $\kappa_{21} = 1.8266$, $\kappa_{22} = 1.6769$ and $\mathfrak{R}_0 \approx 1.0998 > 1$. By Theorem 7.1, we can expect that the drug-endemic equilibrium is globally attractive. In fact, in Figure B.1 (b), $U_{11}(t)$ and $U_{12}(t)$ converge to positive values as time evolves.

9. Discussion

In this paper, we have investigated the global dynamics of the age-structured multi-group heroin epidemic model (1.2). We have obtained $\mathfrak{R}_0$ in connection with the existence of the drug-endemic equilibrium E^* (Theorem 2.1), and shown that $\mathfrak{R}_0$ is the sharp threshold for heroin spreading and vanishing in the sense of the global stability (or attractivity) of each equilibrium: if $\mathfrak{R}_0 < 1$, then the drug-free equilibrium is globally asymptotically stable (Theorem 5.1), and if $\mathfrak{R}_0 > 1$, then the drug-endemic equilibrium is globally attractive (Theorem 7.1).

Since $\mathfrak{R}_0$ completely determines the persistence of the heroin epidemic, social efforts for reducing $\mathfrak{R}_0$ less than 1 have significance in the eradication of the heroin epidemic. As men are about 2 to 3 times more likely to use heroin than women, and young people (18 to 25 year olds) are most at risk of heroin addiction ([30]), it seems reasonable to consider $n = 2$ as in Section 8 and assume that $\beta_{1j}(a) = k\beta_{2j}(a)$, $k \in [2, 3]$, $j \in \{1, 2\}$, and there exists a maximum age of susceptibility $a_\dagger < +\infty$ such that $\beta_{ij}(a) = 0$ for all $a > a_\dagger$ and $i, j \in \{1, 2\}$. In this case, $\mathfrak{R}_0$ is explicitly given by

$$\begin{aligned}\mathfrak{R}_0 =& \frac{1}{2}\Bigg[\frac{k\int_0^{a_\dagger}\beta_{21}(a)S_1^0(a)\mathrm{d}a}{\mu_1+\delta_{11}+(1-\theta_1)p_1} + \frac{\int_0^{a_\dagger}\beta_{22}(a)S_2^0(a)\mathrm{d}a}{\mu_2+\delta_{12}+(1-\theta_2)p_2} \\ &+ \sqrt{\left(\frac{k\int_0^{a_\dagger}\beta_{21}(a)S_1^0(a)\mathrm{d}a}{\mu_1+\delta_{11}+(1-\theta_1)p_1} - \frac{\int_0^{a_\dagger}\beta_{22}(a)S_2^0(a)\mathrm{d}a}{\mu_2+\delta_{12}+(1-\theta_2)p_2}\right)^2 + 4\frac{k\int_0^{a_\dagger}\beta_{22}(a)S_1^0(a)\mathrm{d}a}{\mu_1+\delta_{11}+(1-\theta_1)p_1}\cdot\frac{\int_0^{a_\dagger}\beta_{21}(a)S_2^0(a)\mathrm{d}a}{\mu_2+\delta_{12}+(1-\theta_2)p_2}}\Bigg].\end{aligned}$$

For simplicity, we further assume that $\beta_{2j}(a) = \beta_{2j} > 0$ for all $a \in [0, a_\dagger]$ and $j \in \{1, 2\}$, and investigate the sensitivity of $\mathfrak{R}_0$ to parameters β_{21}, β_{22}, p_1 and p_2 as in [1, Section 3.1.4]. In this case, $\mathfrak{R}_0$ is simplified to

$$\mathfrak{R}_0 = \frac{k\beta_{21}\int_0^{a_\dagger}S_1^0(a)\mathrm{d}a}{\mu_1+\delta_{11}+(1-\theta_1)p_1} + \frac{\beta_{22}\int_0^{a_\dagger}S_2^0(a)\mathrm{d}a}{\mu_2+\delta_{12}+(1-\theta_2)p_2},$$

and the normalized forward sensitivity index for each parameter (see [31]) is calculated as follows.

$$\begin{aligned}A_{\beta_{21}} &= \frac{\beta_{21}}{\mathfrak{R}_0}\frac{\partial\mathfrak{R}_0}{\partial\beta_{21}} = \frac{k}{\mathfrak{R}_0}\frac{\beta_{21}\int_0^{a_\dagger}S_1^0(a)\mathrm{d}a}{\mu_1+\delta_{11}+(1-\theta_1)p_1}, \quad A_{\beta_{22}} = \frac{\beta_{22}}{\mathfrak{R}_0}\frac{\partial\mathfrak{R}_0}{\partial\beta_{22}} = \frac{1}{\mathfrak{R}_0}\frac{\beta_{22}\int_0^{a_\dagger}S_2^0(a)\mathrm{d}a}{\mu_2+\delta_{12}+(1-\theta_2)p_2}, \\ A_{p_1} &= \frac{p_1}{\mathfrak{R}_0}\frac{\partial\mathfrak{R}_0}{\partial p_1} = -\frac{(1-\theta_1)p_1}{\mu_1+\delta_{11}+(1-\theta_1)p_1}A_{\beta_{21}}, \quad A_{p_2} = \frac{p_2}{\mathfrak{R}_0}\frac{\partial\mathfrak{R}_0}{\partial p_2} = -\frac{(1-\theta_2)p_2}{\mu_2+\delta_{12}+(1-\theta_2)p_2}A_{\beta_{22}}.\end{aligned}$$

It always holds that $|A_{\beta_{21}}| > |A_{p_1}|$ and $|A_{\beta_{22}}| > |A_{p_2}|$. Hence, reducing transmission rate β_{21} (resp. β_{22}) is more effective than increasing treatment rate p_1 (resp. p_2). Thus, "prevention is better than cure", proposed in [1, Section 3.1.4], still holds in this sense. However, if $\beta_{21} \approx \beta_{22}$ and each parameter for male is not so different from that for female, then

$$A_{\beta_{21}} \approx kA_{\beta_{22}} \text{ and hence, } |A_{p_1}| \approx k\frac{(1-\theta_1)p_1}{\mu_1+\delta_{11}+(1-\theta_1)p_1}|A_{\beta_{22}}|.$$

Hence, if k is sufficiently large, then we have $|A_{p_1}| > |A_{\beta_{22}}|$ and thus, increasing treatment rate for male is more effective than reducing transmission rate from female to female. This case seems more likely to occur if natural death rate μ_1 and removal rate δ_{11} is much smaller than treatment rate p_1, whereas less likely to occur if $1 - \theta_1$ is small. Since $\theta_1 = \gamma_1/(\mu_1 + \delta_{21} + \gamma_1)$ if $\gamma_1(a) = \gamma_1 > 0$ for all $a \geq 0$, we arrive at the following conclusion: if the rate γ_1 of return to the untreated class of male is large, then $\theta_1 \approx 1$ and prevention is better than cure as stated in [1], whereas if the rate γ_1 is small, then cure of untreated men can be better than prevention of the spread among females.

Finally, we give a remark on $\mathfrak{R}_0$. Since $\mathfrak{R}_0$ determines the persistence of the heroin epidemic, we expect that it could correspond to the basic reproduction number, which is a well-known epidemiological threshold value (see, for instance, [32–34]). As the derivation of $\mathfrak{R}_0$ in this paper is related to the existence of the drug-endemic equilibrium E^*, in a strict sense, it is different from the basic reproduction number, which is defined by the spectral radius of the next generation operator. However, we can expect that $\mathfrak{R}_0$ is equivalent to the basic reproduction number as a threshold value, that is, $\mathfrak{R}_0 > 1$ if and only if the basic reproduction number is greater than 1. We leave the proof for it as a future task.

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Appendix A. MATLAB code for numerical simulation

Function file named bet.m

```
function y=bet (x)
if x<3
    y=0.5;
```

```
else
   y=0;
end
```

Script file for computation of $\mathfrak{R}_0$ and plot of numerical solutions $U_{11}(t)$ and $U_{12}(t)$

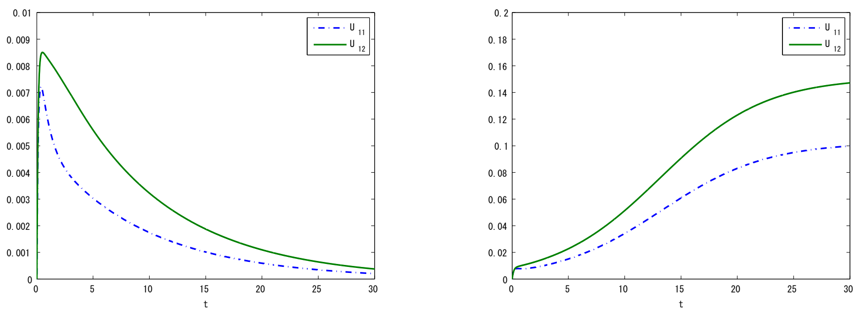
```
n=2;
da=0.01; ae=30; na=ae/da;
for i=1:1:n
    Lam(i)=1+rand;
    mu(i)=1+rand;
    p(i)=0.1*(1+rand);
    d1(i)=0.2*(1+rand);
    d2(i)=0.05*(1+rand);
    gam(i)=5*(1+rand);
    theta(i)=gam(i)/(mu(i)+d2(i)+gam(i));
    for j=1:1:n
        kap(i,j)=1+rand;
    end
    for a=1:1:na
        S0(a,i)=Lam(i)*exp(-mu(i)*a*da);
    end
end
for i=1:1:n
    for j=1:1:n
        for a=1:1:na
            betS0(a,i,j)=kap(i,j)*bet(a*da)*S0(a,i);
        end
        BetS0(i,j)=sum(betS0(:,i,j))*da;
        K(i,j)=BetS0(i,j)/(mu(i)+d1(i)+(1-theta(i))*p(i));
    end
end
R0=max(eig(K))
dt=0.01; te=30; nt=te/dt;
for i=1:1:n
    pS(1,1,i)=Lam(i);
    U1(1,i)=0;
    for a=2:1:na
        pS(1,a,i)=Lam(i)*exp(-mu(i)*a*da);
        U2(1,a,i)=0;
    end
    for a=1:1:na
        S(1,a,i)=pS(1,a,i)/(sum(pS(1,:,i))*da);
        U2(1,a,i)=0.01*S(1,a,i);
    end
end
for t=1:1:nt
    for i=1:1:n
        for a=1:1:na
            for j=1:1:n
                bSU1(t,a,i,j)=kap(i,j)*bet(a*da)*S(t,a,i)*U1(t,j);
                bU1(t,a,i,j)=kap(i,j)*bet(a*da)*U1(t,j);
            end
```

```
            sum_bSU1(t,a,i)=sum(bSU1(t,a,i,:));
            sum_bU1(t,a,i)=sum(bU1(t,a,i,:));
        end
        int_sum_bSU1(t,i)=sum(sum_bSU1(t,:,i))*da;
        int_gU2(t,i)=gam(i)*sum(U2(t,:,i))*da;
    end
    for i=1:1:n
        S(t+1,1,i)=Lam(i);
        U1(t+1,i)=(U1(t,i)+dt*(int_sum_bSU1(t,i)+int_gU2(t,i)))/(1+dt*(mu(i)+d1(i)+p(i)));
        U2(t+1,1,i)=p(i)*U1(t,i);
        for a=2:1:na
            S(t+1,a,i)=(S(t,a,i)+dt*(-(S(t,a,i)-S(t,a-1,i))/da))/(1+dt*(sum_bU1(t,a,i)+mu(i)));
            U2(t+1,a,i)=(U2(t,a,i)+dt*(-(U2(t,a,i)-U2(t,a-1,i))/da))/(1+dt*(mu(i)+d2(i)+gam(i)));
        end
    end
end
T=1:1:nt;
plot(T,U1(T,1),T,U1(T,2))
```

Appendix B. Table and figure

Parameter	Interpretation
Λ_i	Recruitment rate of newborns into group i
μ_i	Natural death rate of individuals in group i
p_i	Treatment rate for drug users in group i
δ_{1i}	Removal rate that includes drug-related deaths of heroin users without treatment in group i
δ_{2i}	Removal rate that includes drug-related deaths of heroin users in treatment and a rate of successful care in group i
$\gamma_i(a)$	Rate of which a treated individual of age a returns to heroin users without treatment class in group i
$\beta_{ij}(a)$	Rate of disease transmission from heroin users without treatment in group j to susceptible individuals of age a in group i

Table B.1: Biological meaning of the parameters in model (1.2).



(a) $\Re_0 \approx 0.9077 < 1$ (b) $\Re_0 \approx 1.0998 > 1$

Figure B.1: Time variation of untreated heroin users $U_{11}(t)$ and $U_{12}(t)$ for different $\Re_0$