

## GLOBAL DYNAMICS OF A GENERAL CLASS OF MULTISTAGE MODELS FOR INFECTIOUS DISEASES\*

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**Abstract.** We propose a general class of multistage epidemiological models that allow possible deterioration and amelioration between any two infected stages. The models can describe disease progression through multiple latent or infectious stages as in the case of HIV and tuberculosis. Amelioration is incorporated into the models to account for the effects of antiretroviral or antibiotic treatment. The models also incorporate general nonlinear incidences and general nonlinear forms of population transfer among stages. Under biologically motivated assumptions, we derive the basic reproduction number  $R_0$  and show that the global dynamics are completely determined by  $R_0$ : if  $R_0 \leq 1$ , the disease-free equilibrium is globally asymptotically stable, and the disease dies out; if  $R_0 > 1$ , then the disease persists in all stages and a unique endemic equilibrium is globally asymptotically stable.

**Key words.** infectious disease progression, amelioration, multiple stages, antiretroviral treatment, HIV, TB, global stability, Lyapunov function

**AMS subject classifications.** 34D23, 92D30

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**1. Introduction.** For infectious diseases that progress through a long infectious period, infectivity or infectiousness can vary significantly in time. Progression of HIV infection can take eight to ten years before the clinical syndrome (AIDS) occurs, and go through several distinct stages, marked by drastically different CD4<sup>+</sup> T-cell counts and viral RNA levels. Infectivity of an infected host is determined by two main factors: the transmission fitness (or transmissibility) of the pathogen inside the host and the frequency at which the host is in contact with others. Transmissibility of the pathogen can vary at different stages of the disease progression according to both the quantity and location of the pathogens inside the host's body. For HIV infection, the first few weeks after seroconversion see an extremely high level of viral load and high transmissibility. This initial stage is followed by a long chronic stage during which viral load is controlled by the immune system and the transmissibility is relatively low. The final stage will see exhaustion of host immune resources and the HIV virus escape from immune control, viral load will explode, and transmissibility will increase. For tuberculosis (TB) infection, the TB bacteria need to develop in the lung to be transmissible through coughing, and their transmissibility depends on their progression in the lung as well as the strength of a host's immune system. Active TB has the highest possibility of developing within the first 2–5 years of infection, while

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most TB infections remain latent for a long period of time until immune compromise occurs due to aging or co-infection with other illnesses such as HIV [5, 28]. It is worthy to note that an infected host's overall infectivity is also impacted significantly by the frequency of the host's contact. During a period of high pathogen transmissibility, a host's infectivity may be low if the host remain isolated or inactive, as may be the case during the late stage of the HIV infection. On the other hand, an asymptomatic disease carrier may have a low pathogen load while maintaining a high infectivity due to risky behaviors.

Medical interventions such as antiretroviral (ART) therapies for HIV and other viral infections and antibiotic treatments for TB and STDs can revert and stop the disease progression. HAART treatment can effectively suppress HIV replication and restore a host's CD4 count. WHO DOTS programs can completely cure patients with active TB. Nonadherence to treatment programs, however, often renders the disease suppression incomplete and results in only partial reverse of the disease progression. Co-infection with other diseases or drug-resistant mutations may lead to much faster disease progression. Medical interventions can reduce the transmissibility factor of an individual host; they may, however, increase the host's infectivity if partial amelioration leads to risky behaviors and more contacts. The overall effect at the population level of individual amelioration brought by medical interventions needs to be carefully investigated using mathematical models.

Variability of infectiousness in time has been described in the literature by Markov chain models or staged progression (SP) models; see, e.g., [19, 21, 22, 24, 34, 36, 42] and the references therein. Progression through long latency is also modelled in the literature using multistage models [2, 10, 11, 23, 37, 47]. In [9], multistage models with a general distribution function for infectious stages were formulated using systems of differential-integral equations. When the distribution of infectious periods is given by an exponential function, the resulting models are described by systems of ordinary differential equations (ODEs). If the distributions are of Gamma type, the resulting models are described as larger systems of ODEs using the "linear chain trick" [10, 35]. Derivation of SP models directly from ODEs can be found in [22]. In [36], amelioration was first incorporated into an SP model for HIV/AIDS with standard incidence. In [15], the global dynamics of an  $n$ -stage SP model with bilinear incidence were analyzed. The effects of vaccine and amelioration on the progression of HIV were discussed in an SP model in [14]. Global dynamics for an SP model with amelioration were further analyzed in [16].

In the present paper, we formulate a general class of multistage models that incorporate disease progression and amelioration of individual hosts to account for more realistic situations. A key new feature in our models is that we allow individual hosts to move with certain probability from any stage of the disease to any other stage either forward (progression) or backward (amelioration). We have also incorporated general nonlinear forms of disease incidence, host demography, and disease progression and amelioration. Our models contain earlier SP models in [15, 16, 22, 29] as special cases. In our models, an infectious stage can be regarded as a latent stage or a quarantine stage if the transmission from that stage is set to zero. Therefore, our models also contain as special cases earlier models with multiple latent stages [2, 13, 23, 37], as well as models with quarantine and relapses [8, 20, 44].

Our main objective is to rigorously establish the global dynamics of this general class of multistage models. Under very general and biologically plausible assumptions on the incidence, birth, and progression functions, we prove that the dynamics of multistage model are completely determined by the basic reproduction number  $R_0$ : if

$R_0 \leq 1$ , the disease-free equilibrium is globally asymptotically stable, and the disease dies out from all stages; if  $R_0 > 1$ , then the disease-free equilibrium is unstable, and the disease persists in all stages. Furthermore, a unique endemic equilibrium is globally asymptotically stable. As is the case for many other complex epidemic models, establishing the uniqueness and global stability of the endemic equilibrium poses a significant mathematical challenge. For earlier models, the proof heavily relies on the bidiagonal or tridiagonal nature of the progression matrix, so that constants for the global Lyapunov functions can be explicitly expressed by inverting the progression matrix. In our model, the progression/amelioration matrix is a full matrix. This fact makes earlier proofs nonapplicable. We demonstrate that a new graph-theoretic approach to the construction of Lyapunov functions developed by the authors [17, 18, 32] allows us to avoid inversion of the progression matrix and successfully establish the global stability. This approach has been shown to work well for complex models with group structures or spatial structures [17, 18, 31, 32, 33, 41, 45, 46]. Our result in this paper is the first to show that the approach also works well for models with general discrete stage structures. While the graph-theoretic approach may be a useful alternative for multistage models in the literature, it is the only approach that is known to work for the general class of models considered in this paper.

We derive our general class of multistage models in section 2. The basic reproduction number is derived in section 3. In section 4, the global stability of the disease-free equilibrium is established. Our main result on global stability of the endemic equilibrium appears in section 5. Two special cases are considered in section 6 to illustrate our main results. A summary and brief discussion are given in section 7.

**2. Model formulation.** To formulate a general multistage disease progression model, we partition the host population into the following compartments: a susceptible compartment  $S$ , a succession of infectious compartments  $I_i, i = 1, 2, \dots, n$ , whose members are in the  $i$ th stage of the disease progression, and a removed compartment  $R$  for individuals who are neglected from the infection process, either because they are in the terminal stage of the disease, such as the stage of AIDS in the case of HIV infection, or they are permanently protected from infection by acquired immunity. Then,  $N = S + I_1 + \dots + I_n$  denotes the total number of individuals who are active in the infection process or the total at-risk population. For any given  $1 \leq i, j \leq n$ , the transfer rate from the  $j$ th stage to the  $i$ th stage is given by a function  $\phi_{ij}(I_j)$ : when  $i > j$ ,  $\phi_{ij}(I_j)$  represents the rate of disease progression or immune deterioration; when  $i < j$ ,  $\phi_{ij}(I_j)$  represents amelioration or immune restoration; assume that  $\phi_{ii} \equiv 0$ . For any given  $1 \leq i \leq n$ , the transfer rate from the  $i$ th stage to the terminal stage of the disease  $R$  is given by  $\phi_{n+1,i}$ .

The disease transmission happens when susceptible individuals contact infective individuals at an infectious stage. The incidence term is of the following general form:

$$(2.1) \quad \sum_{j=1}^n f(N)g_j(S, I_j).$$

Here function  $f(N), N \in (0, \infty)$ , describes density dependence of the incidence. A typical form of function  $f$  is  $f(N) = N^{-\alpha}, 0 \leq \alpha \leq 1$ . Functions  $g_j$  describe the incidence for infections occurred among contacts of  $S$  and  $I_j$ . Possible forms of  $g_j$  are nonlinear incidences  $g_j(S, I_j) = \beta_j S^p I_j^{q_j}$  with constants  $\beta_j, p, q_j > 0$ , and saturation incidences  $g_j(S, I_j) = \frac{\beta_j S^p I_j}{1 + \kappa_j S^p}$  or  $g_j(S, I_j) = \frac{\beta_j S I_j^{q_j}}{1 + \kappa_j I_j^{q_j}}$  with constants  $\beta_j, p_j, q_j > 0$

and  $\kappa_j \geq 0$ . When  $f(N) = N^{-\alpha}$  and  $g_j(S, I_j) = \beta_j S I_j$ , the incidence term in (2.1) becomes  $\frac{\beta_j S I_j}{N^\alpha}$ , which includes the standard incidence when  $\alpha = 1$  and the bilinear incidence when  $\alpha = 0$ .

For demographics of the host population, we assume that, without the disease, the dynamics of the host population is described by the following differential equation:

$$S' = \theta(S).$$

Here function  $\theta(S)$  is any typical growth function with a carrying capacity. Let  $\zeta_i(I_i), 1 \leq i \leq n$ , denote the removal rates of the  $I_i$  compartment, which can include both natural death and death due to the disease infection. When  $\zeta_i = d_i I_i$ , the removal term is customarily called exponential death. Based on the above assumptions and ignoring the removed population in  $R$ , a general multistage model for the population at risk can be formulated as the following system of  $n + 1$  ODEs:

$$\begin{aligned}
 S' &= \theta(S) - f(N) \sum_{j=1}^n g_j(S, I_j), \\
 (2.2) \quad I_1' &= f(N) \sum_{j=1}^n g_j(S, I_j) + \sum_{j=1}^n \phi_{1j}(I_j) - \sum_{j=1}^{n+1} \phi_{j1}(I_1) - \zeta_1(I_1), \\
 I_i' &= \sum_{j=1}^n \phi_{ij}(I_j) - \sum_{j=1}^{n+1} \phi_{ji}(I_i) - \zeta_i(I_i), \quad i = 2, 3, \dots, n.
 \end{aligned}$$

The population transfer among compartments is schematically depicted in the transfer diagram in Figure 1.

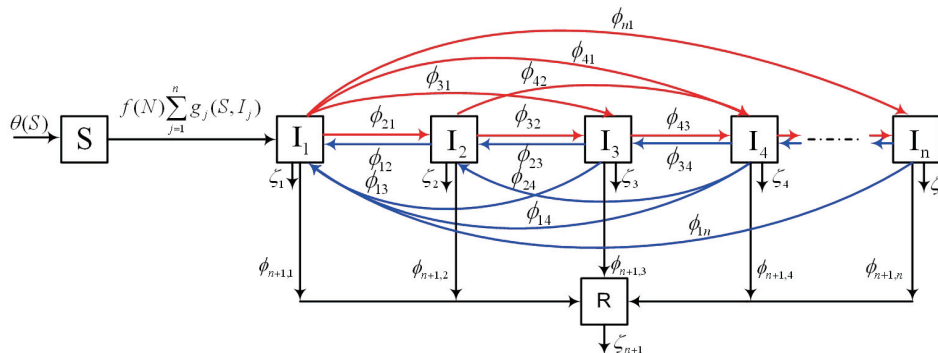


FIG. 1. The transfer diagram for model (2.2). Forward arrows between  $I_j$  compartments indicate disease progression and backward arrows indicate disease amelioration.

Functions  $f(N)$ ,  $g_j(S, I_j)$ ,  $\zeta_i(I_i)$ , and  $\phi_{ij}(I_j)$  are assumed to be sufficiently smooth so that solutions to (2.2) with nonnegative initial conditions exist and are unique. Throughout the paper, we make the following basic and biologically motivated assumptions:

- (H<sub>1</sub>) There exists  $\bar{S} > 0$  such that  $\theta(\bar{S}) = 0$  and  $\theta(S)(S - \bar{S}) < 0$  for all  $S \geq 0$  and  $S \neq \bar{S}$ .
- (H<sub>2</sub>) For all  $N > 0$ ,  $f(N) > 0$  and  $f(N)$  is nonincreasing.
- (H<sub>3</sub>) For  $1 \leq j \leq n$ ,  $g_j(S, I_j) \geq 0$  for all  $S, I_j \geq 0$ , and  $g_j(0, I_j) = g_j(S, 0) = 0$ .

- (H<sub>4</sub>) For  $1 \leq i, j \leq n$ ,  $\phi_{ij}(I_j) \geq 0$  for  $I_j \geq 0$ ;  $\sum_{j=1}^n \phi_{ji}(I_i) = 0$  if and only if  $I_i = 0$ .
- (H<sub>5</sub>) For  $1 \leq i \leq n$ ,  $\zeta_i(0) = 0$ ; there exists constant  $d_i > 0$  such that  $\zeta_i(I_i) \geq d_i I_i$  for all  $I_i \geq 0$ .

Assumption (H<sub>1</sub>) ensures that the host population has carrying capacity  $\bar{S} > 0$  when the disease is absent. A common form of  $\theta$  is

$$\theta(S) = \Lambda + rS\left(1 - \frac{S}{K}\right) - dS,$$

in which case  $\bar{S}$  is the positive root of the quadratic equation

$$\frac{rS^2}{K} - (r - d)S - \Lambda = 0.$$

This form of  $\theta(S)$  includes many simple demographic functions: immigration with exponential death,  $\Lambda - dS$ , and logistic growth in the host population, which may be more realistic for animal diseases. For biological considerations, we are interested in solutions that are nonnegative and bounded. It can be verified that solutions of (2.2) starting with nonnegative initial conditions stay nonnegative for all  $t \geq 0$ . Furthermore, from the first equations of (2.2), we know that  $S'(t) \leq \theta(S)$ , and thus,  $\limsup_{t \rightarrow \infty} S(t) \leq \bar{S}$  by assumption (H<sub>1</sub>). Assumption (H<sub>5</sub>) is required to ensure the total population remains bounded. In fact, adding all equations of (2.2) yields that  $(S + I_1 + \dots + I_n)' = \theta(S) - \zeta_1(I_1) - \dots - \zeta_n(I_n)$ . Let

$$d^* = \min\{d_i : 1 \leq i \leq n\} > 0$$

and choose  $M$  sufficiently large such that  $M \geq d^* \bar{S} + \max_{S \in [0, \bar{S}]} \theta(S)$ . Then, we obtain

$$(S + I_1 + \dots + I_n)' \leq \max_{S \in [0, \bar{S}]} \theta(S) - d_1 I_1 - \dots - d_n I_n \leq M - d^*(S + I_1 + \dots + I_n),$$

which implies that  $\limsup_{t \rightarrow \infty} (S + I_1 + \dots + I_n) \leq \frac{M}{d^*}$ . Therefore, all solutions are bounded and the feasible region for model (2.2) can be taken as

$$(2.3) \quad \Gamma = \left\{ (S, I_1, \dots, I_n) \in \mathbb{R}_+^{n+1} \mid S \leq \bar{S}, S + I_1 + \dots + I_n \leq \frac{M}{d^*} \right\}.$$

It can be verified that  $\Gamma$  is positively invariant with respect to (2.2).

Assumption (H<sub>2</sub>) is satisfied by the class of functions  $f(N) = N^{-\alpha}$ ,  $0 \leq \alpha \leq 1$ . Assumption (H<sub>3</sub>) allows the possibility of  $g_i \equiv 0$  for some stages while requiring that overall transmission is nonzero. With this generality, some stages can be interpreted as latent or quarantined. Assumption (H<sub>4</sub>) implies that transfers out of a stage  $i$  is nonzero while transfers into the stage may be zero. This ensures the disease progresses through all the  $I_j$  stages and the only terminal stage is  $R$ .

Disease progression and amelioration are described in our model by the transfer matrix  $\{\phi_{ij}\}$ . In the special case when the progression is given by  $\phi_{ij}(I_j) = \gamma_{ij} I_j$ ,  $i > j$ , and the amelioration given by  $\phi_{ij}(I_j) = \delta_{ij} I_j$ ,  $i < j$ , the transfer matrix can be represented by

$$(2.4) \quad A = \begin{pmatrix} 0 & \delta_{12} & \cdots & \delta_{1n} \\ \gamma_{21} & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \delta_{(n-1)n} \\ \gamma_{n1} & \cdots & \gamma_{n(n-1)} & 0 \end{pmatrix}.$$

In earlier multistage models in the literature, disease progression or amelioration proceeds only to the next or previous stage. Correspondingly, transfer matrix  $A$  is typically tridiagonal [2, 14, 15, 16, 22, 23, 36, 39]. In our model, we allow the transfer matrix to be a full matrix.

For notational convenience, we set

$$(2.5) \quad \psi_i(I_i) = \sum_{j=1}^{n+1} \phi_{ji}(I_i) + \zeta_i(I_i), \quad 1 \leq i \leq n.$$

Then, assumption  $(H_4)$  implies that  $\psi_i(I_i) = 0$  if and only if  $I_i = 0$ , for  $i = 1, \dots, n$ . We can rewrite model (2.2) in the following form:

$$(2.6) \quad \begin{aligned} S' &= \theta(S) - f(N) \sum_{j=1}^n g_j(S, I_j), \\ I_1' &= f(N) \sum_{j=1}^n g_j(S, I_j) + \sum_{j=1}^n \phi_{1j}(I_j) - \psi_1(I_1), \\ I_i' &= \sum_{j=1}^n \phi_{ij}(I_j) - \psi_i(I_i), \quad i = 2, 3, \dots, n. \end{aligned}$$

**3. Equilibria and the basic reproduction number.** Since  $\theta(S) = 0$  has a unique positive solution  $\bar{S}$  and  $g_j(S, 0) = 0$ ,  $\phi_{ij}(0) = 0$ ,  $\psi_i(0) = \sum_{j=1}^{n+1} \phi_{ji}(0) + \zeta_i(0) = 0$  for all  $i, j$ , system (2.6) has a unique *disease-free equilibrium*  $P_0 = (\bar{S}, 0, \dots, 0)$ . A positive equilibrium of (2.6), if one exists, is called an *endemic equilibrium*, and denoted by  $P^* = (S^*, I_1^*, \dots, I_n^*)$ , where  $S^*, I_1^*, \dots, I_n^* > 0$  satisfy the following equilibrium equations:

$$(3.1) \quad \begin{aligned} \theta(S^*) &= f(N^*) \sum_{j=1}^n g_j(S^*, I_j^*), \\ \psi_1(I_1^*) &= f(N^*) \sum_{j=1}^n g_j(S^*, I_j^*) + \sum_{j=1}^n \phi_{1j}(I_j^*), \\ \psi_i(I_i^*) &= \sum_{j=1}^n \phi_{ij}(I_j^*), \quad i = 2, 3, \dots, n, \\ N^* &= S^* + \sum_{j=1}^n I_j^*. \end{aligned}$$

In order to derive the basic reproduction number, we make the following assumptions on the behaviors of functions  $g_i(S, I_i)$ ,  $\phi_{ij}(I_i)$ , and  $\psi_i(I_i)$  near  $I_i = 0$ .

$(H_6)$  There exist constants  $0 \leq c_i \leq \infty$ ,  $1 \leq i \leq n$ , and  $\max_i \{c_i\} > 0$  such that

$$\lim_{I_i \rightarrow 0^+} \frac{g_i(\bar{S}, I_i)}{\psi_i(I_i)} = c_i.$$

$(H_7)$  There exist constants  $0 \leq b_{ij} < \infty$ ,  $1 \leq i, j \leq n$ , such that  $\lim_{I_j \rightarrow 0^+} \frac{\phi_{ij}(I_j)}{\psi_j(I_j)} = b_{ij}$ .

$(H_8)$  For  $1 \leq i \leq n$ ,  $\liminf_{I_i \rightarrow 0^+} \frac{I_i}{\psi_i(I_i)} > 0$ .

Let

$$E = \begin{pmatrix} f(\bar{S})c_1 & f(\bar{S})c_2 & \dots & f(\bar{S})c_n \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 0 \end{pmatrix}$$

and

$$(3.2) \quad B = \begin{pmatrix} 1 & -b_{12} & \dots & -b_{1n} \\ -b_{21} & 1 & \dots & -b_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -b_{n1} & -b_{n2} & \dots & 1 \end{pmatrix}.$$

Since  $\psi_i(I_i) \geq \sum_{j=1}^{n+1} \phi_{ji}(I_i) + d_i I_i$  for each  $i$ , by assumption  $(H_8)$  we have  $\sum_{i=1}^n b_{ij} < 1$ , and thus  $B$  is diagonally dominant in rows. Therefore,  $B$  is a nonsingular  $M$ -matrix and its inverse  $B^{-1}$  is nonnegative [3, p. 137]. Following [1, 6], the basic reproduction number is defined as the spectral radius of the nonnegative matrix  $EB^{-1}$ ,

$$(3.3) \quad R_0 = \rho(EB^{-1}).$$

If functions  $g_i, \phi_{ij}, \psi_i$  are differentiable, then the method in [43] can be used to derive  $R_0$ . Let

$$F = \begin{pmatrix} f(\bar{S})\frac{\partial g_1}{\partial I_1}(\bar{S}, 0) & f(\bar{S})\frac{\partial g_2}{\partial I_2}(\bar{S}, 0) & \dots & f(\bar{S})\frac{\partial g_n}{\partial I_n}(\bar{S}, 0) \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \psi'_1(0) & -\phi'_{12}(0) & \dots & -\phi'_{1n}(0) \\ -\phi'_{21}(0) & \psi'_2(0) & \dots & -\phi'_{2n}(0) \\ \vdots & \vdots & \ddots & \vdots \\ -\phi'_{n1}(0) & -\phi'_{n2}(0) & \dots & \psi'_n(0) \end{pmatrix}.$$

Then  $R_0 = \rho(FV^{-1})$  using the definition in [43]. Note that  $\psi'_i(0) \geq d_i > 0$  for each  $i$  by assumption  $(H_5)$ . Let  $D = \text{diag}\{\frac{1}{\psi'_1(0)}, \dots, \frac{1}{\psi'_n(0)}\}$ . Then  $D$  is invertible, and  $FV^{-1} = FD(VD)^{-1} = EB^{-1}$ . This relation shows that the two definitions of  $R_0$  are equivalent.

In the special case when  $g_i(S, I_i) = \beta_i S I_i$ ,  $\phi_{ij}(I_j) = \delta_{ij} I_j$ , and  $\zeta_i(I_i) = d_i I_i$ , assumptions  $(H_6)$  and  $(H_7)$  are satisfied with

$$(3.4) \quad c_i = \frac{\beta_i \bar{S}}{\sum_{j=1}^{n+1} \delta_{ji} + d_i} \geq 0, \quad b_{ij} = \frac{\delta_{ij}}{\sum_{k=1}^{n+1} \delta_{kj} + d_j} \geq 0.$$

One can verify that the basic reproduction number  $R_0$  defined above includes special cases of  $R_0$  defined for simpler forms of multistage models in the literature.

**4. Global dynamics when  $R_0 \leq 1$ .** In this section, we show that the disease dies out when the basic reproduction number  $R_0 \leq 1$ , and that the disease persists otherwise. We make the following assumptions.

- (A<sub>1</sub>) For  $1 \leq i \leq n$ ,  $f(S)g_i(S, I_i) \leq f(\bar{S})g_i(\bar{S}, I_i)$  holds for all  $0 \leq S \leq \bar{S}, I_i \geq 0$ ; if  $f(S)g_i(S, I_i) = f(\bar{S})g_i(\bar{S}, I_i) \neq 0$ , then  $S = \bar{S}$ ; for  $I_i > 0$ ,  $\frac{g_i(\bar{S}, I_i)}{\psi_i(I_i)} \leq c_i$ .
- (A<sub>2</sub>) For all  $I_j > 0, 1 \leq i, j \leq n$ ,  $\sup_{I_j > 0} \frac{\phi_{ij}(I_j)}{\psi_j(I_j)} = b_{ij}$ .

**THEOREM 4.1.** *Suppose that assumptions (H<sub>1</sub>)–(H<sub>8</sub>) hold. If  $R_0 \leq 1$  and assumptions (A<sub>1</sub>) and (A<sub>2</sub>) hold, then the disease-free equilibrium  $P_0$  is globally asymptotically stable in  $\Gamma$ ; if  $R_0 > 1$ , then  $P_0$  is unstable and system (2.6) is uniformly persistent in the interior  $\overset{\circ}{\Gamma}$  of  $\Gamma$ .*

*Proof.* Let matrix  $B$  be as defined in (3.2) and

$$(w_1, w_2, \dots, w_n) = f(\bar{S})(c_1, c_2, \dots, c_n)B^{-1} \geq 0.$$

Then, by (3.2) and (3.3),  $w_1 = R_0 \leq 1$ . Define a Lyapunov function

$$L = \sum_{i=1}^n w_i I_i.$$

The derivative of  $L$  along solutions of system (2.6) is

$$\begin{aligned} \dot{L} &= w_1 f(N) \sum_{j=1}^n g_j(S, I_j) + \sum_{i=1}^n w_i \left( \sum_{j=1}^n \phi_{ij}(I_j) - \psi_i(I_i) \right) \\ &= w_1 f(N) \left( \frac{g_1(S, I_1)}{\psi_1(I_1)}, \frac{g_2(S, I_2)}{\psi_2(I_2)}, \dots, \frac{g_n(S, I_n)}{\psi_n(I_n)} \right) (\psi_1(I_1), \dots, \psi_n(I_n))^T \\ &\quad - (w_1, \dots, w_n) \begin{pmatrix} 1 & -\frac{\phi_{12}(I_2)}{\psi_2(I_2)} & \dots & -\frac{\phi_{1n}(I_n)}{\psi_n(I_n)} \\ -\frac{\phi_{21}(I_1)}{\psi_1(I_1)} & 1 & \dots & -\frac{\phi_{2n}(I_n)}{\psi_n(I_n)} \\ \vdots & \vdots & \ddots & \vdots \\ -\frac{\phi_{n1}(I_1)}{\psi_1(I_1)} & -\frac{\phi_{n2}(I_2)}{\psi_2(I_2)} & \dots & 1 \end{pmatrix} (\psi_1(I_1), \dots, \psi_n(I_n))^T \\ &\leq w_1 f(\bar{S})(c_1, \dots, c_n)(\psi_1(I_1), \dots, \psi_n(I_n))^T - (w_1, \dots, w_n)B(\psi_1(I_1), \dots, \psi_n(I_n))^T \\ &= (w_1 - 1)f(\bar{S})(c_1, \dots, c_n)(\psi_1(I_1), \dots, \psi_n(I_n))^T \leq 0, \quad \text{since } w_1 = R_0 \leq 1. \end{aligned}$$

Therefore, all limit points are contained in the largest invariant subset  $K$  of

$$G = \{(S, I_1, \dots, I_n) \in \Gamma \mid \dot{L} = 0\}.$$

Suppose that  $R_0 < 1$ . Then  $\dot{L} = 0$  implies that  $\sum_{i=1}^n c_i \psi_i(I_i) = 0$ . Using assumption (A<sub>1</sub>), this implies that  $\sum_{j=1}^n g_j(S, I_j) = 0$  holds along solutions in  $K$ . Using the  $S$  equation in (2.6) we obtain that  $S = \bar{S}$  in  $K$ . Furthermore, from equations of  $I_i$ , we have

$$\left( \sum_{i=1}^n I_i \right)' = - \sum_{i=1}^n \zeta_i(I_i) - \sum_{j=1}^n \phi_{(n+1)j}(I_j) \leq -d^* \sum_{i=1}^n I_i.$$

Therefore, along any solution in  $K$ , we necessarily have  $S = \bar{S}$  and  $I_1 = \dots = I_n = 0$ . As a consequence,  $K = \{P_0\}$  if  $R_0 < 1$ .



If  $R_0 = 1$ , then  $\dot{L} = 0$  implies

$$f(S) \left( \frac{g_1(S, I_1)}{\psi_1(I_1)}, \frac{g_2(S, I_2)}{\psi_2(I_2)}, \dots, \frac{g_n(S, I_n)}{\psi_n(I_n)} \right) (\psi_1(I_1), \dots, \psi_n(I_n))^T = f(\bar{S})(c_1, \dots, c_n) (\psi_1(I_1), \dots, \psi_n(I_n))^T.$$

Therefore, there exists  $1 \leq i \leq n$  such that

$$\frac{f(S)g_i(S, I_i)}{\psi_i(I_i)} = \frac{f(\bar{S})g_i(\bar{S}, I_i)}{\psi_i(I_i)} = c_i > 0, \quad \text{namely,}$$

$$f(S)g_i(S, I_i) = f(\bar{S})g_i(\bar{S}, I_i) \neq 0 \quad \text{for all } I_i > 0.$$

By assumption  $(A_1)$ , we have  $S = \bar{S}$ . Using the  $S$  equation in (2.6), we know that  $\sum_{j=1}^n g_j(S, I_j) = 0$  holds along any solution in  $K$ . The same argument as in the previous case shows that  $K = \{P_0\}$  if  $R_0 = 1$  as well. By LaSalle’s invariance principle [27],  $P_0$  is globally asymptotically stable in  $\Gamma$  if  $R_0 \leq 1$ .

If  $R_0 > 1$ , then, by continuity,  $\dot{L} > 0$  in a neighborhood of  $P_0$  in  $\overset{\circ}{\Gamma}$ . Solutions in  $\mathbb{R}_+^{n+1}$  sufficiently close to  $P_0$  move away from  $P_0$ , except those on the invariant  $S$ -axis. This implies that  $P_0$  is unstable. Using a uniform persistence result from [12] and a similar argument as in the proof of Proposition 3.3 of [30], we can show that, when  $R_0 > 1$ , the instability of  $P_0$  implies the uniform persistence of (2.6). This completes the proof of Theorem 4.1.  $\square$

Uniform persistence of (2.6) and the positive invariance of compact set  $\Gamma$  imply the existence of an equilibrium of (2.6) in  $\overset{\circ}{\Gamma}$  (see Theorem D.3 in [40] or Theorem 2.8.6 in [4]).

PROPOSITION 4.2. *Suppose that assumptions  $(H_1)$ – $(H_8)$  hold. If  $R_0 > 1$ , then there exists at least one endemic equilibrium for system (2.6).*

Theorem 4.1 and Proposition 4.2 imply that the disease always dies out from all stages if the basic reproduction number  $R_0 \leq 1$ , irrespective of the size of the initial outbreak. If  $R_0 > 1$ , then the disease persists in all stages and it can persist at a constant endemic state. This establishes  $R_0$  as a sharp threshold for the disease persistence.

**5. Global dynamics when  $R_0 > 1$ .** In this section, for the special case  $f(N) \equiv 1$ , we show that the endemic equilibrium is unique and is globally asymptotically stable in the interior of the feasible region  $\Gamma$ . Biologically, this implies that the disease always becomes endemic and persists at a unique endemic equilibrium, no matter how small the size of the initial outbreak is. Suppose that assumptions  $(H_1)$ – $(H_8)$  hold. By Proposition 4.2, an endemic equilibrium  $P^* = (S^*, I_1^*, \dots, I_n^*)$  exists. Here  $S^*, I_1^*, \dots, I_n^*$  are positive and satisfy the equilibrium equations (3.1).

Assume that there exists a function  $\Phi : \mathbb{R}_+ \rightarrow \mathbb{R}_+$  such that the following assumptions hold.

(B<sub>1</sub>) For  $S \neq S^*$ ,

$$(\theta(S) - \theta(S^*))(\Phi(S) - \Phi(S^*)) < 0.$$

(B<sub>2</sub>) For  $0 \leq S \leq \bar{S}, I_j > 0, 1 \leq j \leq n$ ,

$$\left( \frac{g_j(S, I_j)}{\Phi(S)} - \frac{g_j(S^*, I_j^*)}{\Phi(S^*)} \right) \left( \frac{g_j(S, I_j)}{\Phi(S)\psi_j(I_j)} - \frac{g_j(S^*, I_j^*)}{\Phi(S^*)\psi_j(I_j^*)} \right) \leq 0.$$

(B<sub>3</sub>) For  $I_j > 0, 1 \leq i, j \leq n$ ,

$$(\phi_{ij}(I_j) - \phi_{ij}(I_j^*)) \cdot \left( \frac{\phi_{ij}(I_j)}{\psi_j(I_j)} - \frac{\phi_{ij}(I_j^*)}{\psi_j(I_j^*)} \right) \leq 0.$$

We also make the following monotonicity assumption.

(B<sub>4</sub>) For each  $1 \leq i \leq n$ , one of the functions  $g_i(S^*, I_i), \sum_{j=1}^n \phi_{ij}(I_j), \psi_i(I_i)$  is strictly monotone in  $I_i$ .

We define a matrix  $M = (m_{ij})$ , where

$$(5.1) \quad m_{ij} = \begin{cases} \phi_{1j}(I_j^*) + g_j(S^*, I_j^*) & \text{if } i = 1, \\ \phi_{ij}(I_j^*) & \text{if } i \geq 2. \end{cases}$$

We regard matrix  $M$  as a weight matrix for the infection-transfer graph  $G$  of our model, as shown in Figure 2. In the weighted graph  $G$ , solid arrows indicate transfers of individuals between compartments, and dashed arrows indicate infection. For our next result, we will require that  $M$  be an irreducible matrix. In graph-theoretic terms, irreducibility of  $M$  is equivalent to weighted graph  $(G, M)$  being strongly connected [3].

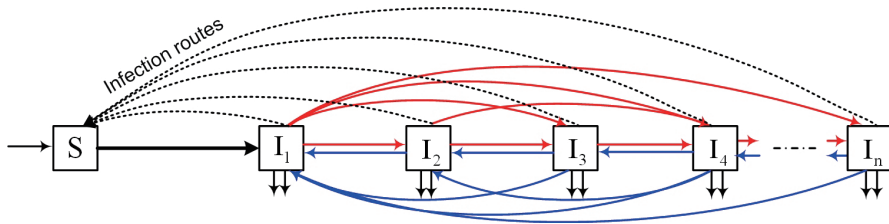


FIG. 2. The infection-transfer graph  $G$  at the endemic equilibrium  $P^*$  of model (2.2). Solid arrows indicate transfers of individuals between compartments, and dashed arrows indicate infection.

**THEOREM 5.1.** *Suppose that assumptions (H<sub>1</sub>)–(H<sub>8</sub>) hold and that  $f(N) \equiv 1$ . Assume that matrix  $M$  defined in (5.1) is irreducible, and that assumptions (B<sub>1</sub>)–(B<sub>4</sub>) hold. Then, when  $R_0 > 1$ , there exists a unique endemic equilibrium  $P^*$  and it is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ .*

*Proof.* For system (2.6), we consider the following Lyapunov function:

$$(5.2) \quad V = \tau_1 \int_{S^*}^S \frac{\Phi(\xi) - \Phi(S^*)}{\Phi(\xi)} d\xi + \sum_{i=1}^n \tau_i \int_{I_i^*}^{I_i} \frac{\psi_i(\xi) - \psi_i(I_i^*)}{\psi_i(\xi)} d\xi.$$

Here  $\tau_i > 0, i = 1, \dots, n$ , are constants to be specified later. Differentiating  $V$  along solutions of (2.6) and using equilibrium equations (3.1) to simplify, we obtain

$$\begin{aligned}
 (5.3) \quad \dot{V} &= \tau_1 \left( \theta(S) - \theta(S) \frac{\Phi(S^*)}{\Phi(S)} + \sum_{j=1}^n g_j(S, I_j) \frac{\Phi(S^*)}{\Phi(S)} + \sum_{j=1}^n \phi_{ij}(I_j) - \psi_1(I_1) \right. \\
 &\quad \left. - \sum_{j=1}^n g_j(S, I_j) \frac{\psi_1(I_1^*)}{\psi_1(I_1)} - \sum_{j=1}^n \phi_{ij}(I_j) \frac{\psi_1(I_1^*)}{\psi_1(I_1)} + \psi_1(I_1^*) \right) \\
 &\quad + \sum_{i=2}^n \tau_i \left( \sum_{j=1}^n \phi_{ij}(I_j) - \psi_i(I_i) - \sum_{j=1}^n \phi_{ij}(I_j) \frac{\psi_i(I_i^*)}{\psi_i(I_i)} + \psi_i(I_i^*) \right) \\
 &= \tau_1 (\theta(S) - \theta(S^*)) \left( 1 - \frac{\Phi(S^*)}{\Phi(S)} \right) \\
 &\quad + \tau_1 \sum_{j=1}^n g_j(S^*, I_j^*) \left( 2 + \frac{g_j(S, I_j) \Phi(S^*)}{g_j(S^*, I_j^*) \Phi(S)} - \frac{\Phi(S^*)}{\Phi(S)} - \frac{\psi_1(I_1)}{\psi_1(I_1^*)} - \frac{g_j(S, I_j) \psi_1(I_1^*)}{g_j(S^*, I_j^*) \psi_1(I_1)} \right) \\
 &\quad + \sum_{i=1}^n \tau_i \sum_{j=1}^n \phi_{ij}(I_j^*) \left( \frac{\phi_{ij}(I_j)}{\phi_{ij}(I_j^*)} - \frac{\psi_i(I_i)}{\psi_i(I_i^*)} - \frac{\phi_{ij}(I_j) \psi_i(I_i^*)}{\phi_{ij}(I_j^*) \psi_i(I_i)} + 1 \right).
 \end{aligned}$$

By assumption (B<sub>1</sub>), we have

$$(5.4) \quad (\theta(S) - \theta(S^*)) \left( 1 - \frac{\Phi(S^*)}{\Phi(S)} \right) \leq 0.$$

Using assumption (B<sub>3</sub>) we obtain

$$\begin{aligned}
 (5.5) \quad &\frac{\phi_{ij}(I_j)}{\phi_{ij}(I_j^*)} - \frac{\psi_i(I_i)}{\psi_i(I_i^*)} - \frac{\phi_{ij}(I_j) \psi_i(I_i^*)}{\phi_{ij}(I_j^*) \psi_i(I_i)} + 1 = \left( \frac{\phi_{ij}(I_j)}{\phi_{ij}(I_j^*)} - 1 \right) \left( 1 - \frac{\phi_{ij}(I_j^*) \psi_j(I_j)}{\phi_{ij}(I_j) \psi_j(I_j^*)} \right) \\
 &+ \left( 1 - \frac{\phi_{ij}(I_j) \psi_i(I_i^*)}{\phi_{ij}(I_j^*) \psi_i(I_i)} + \ln \frac{\phi_{ij}(I_j) \psi_i(I_i^*)}{\phi_{ij}(I_j^*) \psi_i(I_i)} \right) \\
 &+ \left( 1 - \frac{\phi_{ij}(I_j^*) \psi_j(I_j)}{\phi_{ij}(I_j) \psi_j(I_j^*)} + \ln \frac{\phi_{ij}(I_j^*) \psi_j(I_j)}{\phi_{ij}(I_j) \psi_j(I_j^*)} \right) \\
 &+ \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \ln \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \frac{\psi_i(I_i)}{\psi_i(I_i^*)} + \ln \frac{\psi_i(I_i)}{\psi_i(I_i^*)} \\
 &\leq 1 - \frac{\phi_{ij}(I_j) \psi_i(I_i^*)}{\phi_{ij}(I_j^*) \psi_i(I_i)} + \ln \frac{\phi_{ij}(I_j) \psi_i(I_i^*)}{\phi_{ij}(I_j^*) \psi_i(I_i)} \\
 &+ 1 - \frac{\phi_{ij}(I_j^*) \psi_j(I_j)}{\phi_{ij}(I_j) \psi_j(I_j^*)} + \ln \frac{\phi_{ij}(I_j^*) \psi_j(I_j)}{\phi_{ij}(I_j) \psi_j(I_j^*)} \\
 &+ \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \ln \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \frac{\psi_i(I_i)}{\psi_i(I_i^*)} + \ln \frac{\psi_i(I_i)}{\psi_i(I_i^*)}.
 \end{aligned}$$

Similarly, using inequality (B<sub>2</sub>), we obtain

$$\begin{aligned}
 (5.6) \quad & 2 + \frac{g_j(S, I_j)\Phi(S^*)}{g_j(S^*, I_j^*)\Phi(S)} - \frac{\Phi(S^*)}{\Phi(S)} - \frac{\psi_1(I_1)}{\psi_1(I_1^*)} - \frac{g_j(S, I_j)\psi_1(I_1^*)}{g_j(S^*, I_j^*)\psi_1(I_1)} \\
 & = \left( \frac{g_j(S, I_j)\Phi(S^*)}{g_j(S^*, I_j^*)\Phi(S)} - 1 \right) \left( 1 - \frac{g_j(S^*, I_j^*)\Phi(S)\psi_j(I_j)}{g_j(S, I_j)\Phi(S^*)\psi_j(I_j^*)} \right) \\
 & \quad + \left( 1 - \frac{\Phi(S^*)}{\Phi(S)} + \ln \frac{\Phi(S^*)}{\Phi(S)} \right) + \left( 1 - \frac{g_j(S, I_j)\psi_1(I_1^*)}{g_j(S^*, I_j^*)\psi_1(I_1)} + \ln \frac{g_j(S, I_j)\psi_1(I_1^*)}{g_j(S^*, I_j^*)\psi_1(I_1)} \right) \\
 & \quad + \left( 1 - \frac{g_j(S^*, I_j^*)\Phi(S)\psi_j(I_j)}{g_j(S, I_j)\Phi(S^*)\psi_j(I_j^*)} + \ln \frac{g_j(S^*, I_j^*)\Phi(S)\psi_j(I_j)}{g_j(S, I_j)\Phi(S^*)\psi_j(I_j^*)} \right) \\
 & \quad + \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \ln \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \frac{\psi_1(I_1)}{\psi_1(I_1^*)} + \ln \frac{\psi_1(I_1)}{\psi_1(I_1^*)} \\
 & \leq \left( 1 - \frac{\Phi(S^*)}{\Phi(S)} + \ln \frac{\Phi(S^*)}{\Phi(S)} \right) + \left( 1 - \frac{g_j(S, I_j)\psi_1(I_1^*)}{g_j(S^*, I_j^*)\psi_1(I_1)} + \ln \frac{g_j(S, I_j)\psi_1(I_1^*)}{g_j(S^*, I_j^*)\psi_1(I_1)} \right) \\
 & \quad + \left( 1 - \frac{g_j(S^*, I_j^*)\Phi(S)\psi_j(I_j)}{g_j(S, I_j)\Phi(S^*)\psi_j(I_j^*)} + \ln \frac{g_j(S^*, I_j^*)\Phi(S)\psi_j(I_j)}{g_j(S, I_j)\Phi(S^*)\psi_j(I_j^*)} \right) \\
 & \quad + \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \ln \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \frac{\psi_1(I_1)}{\psi_1(I_1^*)} + \ln \frac{\psi_1(I_1)}{\psi_1(I_1^*)}.
 \end{aligned}$$

Combining (5.3)–(5.6) and using the definition of  $m_{ij}$  in (5.1), we obtain

$$\begin{aligned}
 (5.7) \quad \dot{V} & \leq \sum_{i=1}^n \tau_i \sum_{j=1}^n \phi_{ij}(I_j^*) \left[ 1 - \frac{\phi_{ij}(I_j)\psi_i(I_i^*)}{\phi_{ij}(I_j^*)\psi_i(I_i)} + \ln \frac{\phi_{ij}(I_j)\psi_i(I_i^*)}{\phi_{ij}(I_j^*)\psi_i(I_i)} \right] \\
 & \quad + \sum_{i=1}^n \tau_i \sum_{j=1}^n \phi_{ij}(I_j^*) \left[ 1 - \frac{\phi_{ij}(I_j^*)\psi_j(I_j)}{\phi_{ij}(I_j)\psi_j(I_j^*)} + \ln \frac{\phi_{ij}(I_j^*)\psi_j(I_j)}{\phi_{ij}(I_j)\psi_j(I_j^*)} \right] \\
 & \quad + \tau_1 \sum_{j=1}^n g_j(S^*, I_j^*) \left[ 1 - \frac{\Phi(S^*)}{\Phi(S)} + \ln \frac{\Phi(S^*)}{\Phi(S)} \right] \\
 & \quad + \tau_1 \sum_{j=1}^n g_j(S^*, I_j^*) \left[ 1 - \frac{g_j(S, I_j)\psi_1(I_1^*)}{g_j(S^*, I_j^*)\psi_1(I_1)} + \ln \frac{g_j(S, I_j)\psi_1(I_1^*)}{g_j(S^*, I_j^*)\psi_1(I_1)} \right] \\
 & \quad + \tau_1 \sum_{j=1}^n g_j(S^*, I_j^*) \left[ 1 - \frac{g_j(S^*, I_j^*)\Phi(S)\psi_j(I_j)}{g_j(S, I_j)\Phi(S^*)\psi_j(I_j^*)} + \ln \frac{g_j(S^*, I_j^*)\Phi(S)\psi_j(I_j)}{g_j(S, I_j)\Phi(S^*)\psi_j(I_j^*)} \right] \\
 & \quad + \sum_{i=1}^n \tau_i \sum_{j=1}^n m_{ij} \left( \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \ln \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \frac{\psi_i(I_i)}{\psi_i(I_i^*)} + \ln \frac{\psi_i(I_i)}{\psi_i(I_i^*)} \right).
 \end{aligned}$$

Note that function  $s(x) = 1 - x + \ln x$  is nonpositive for  $x > 0$  and  $s(x) = 0$  if and only if  $x = 1$ . We see that expressions enclosed in the square brackets in (5.7) are negative definite. To show that  $\dot{V}$  negative definite, we choose constants  $\tau_i > 0$  such that the last expression in (5.7) vanishes. Let  $M$  be the infection-transfer matrix defined in (5.1) and let

$$L(M) = \text{diag} \left( \sum_{j=1}^n m_{1j}, \dots, \sum_{j=1}^n m_{nj} \right) - M$$

be the algebraic Laplacian matrix of  $M$ . We choose  $\tau_i$  as the co-factor of the  $i$ th diagonal entry of  $L(M)$ . By Kirchhoff’s matrix tree theorem (see the appendix), since

$M$  is irreducible, we know that  $\tau_i > 0$ . Furthermore, using the tree cycle identity and its corollary in the appendix, we obtain the following identity:

$$\sum_{i=1}^n \tau_i \sum_{j=1}^n m_{ij} \left( \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \ln \frac{\psi_j(I_j)}{\psi_j(I_j^*)} - \frac{\psi_i(I_i)}{\psi_i(I_i^*)} + \ln \frac{\psi_i(I_i)}{\psi_i(I_i^*)} \right) \equiv 0.$$

Therefore, we conclude that  $\dot{V} \leq 0$  for all  $(S, I_1, \dots, I_n) \in \overset{\circ}{\Gamma}$ . Furthermore,  $\dot{V} = 0$  implies that

$$(5.8) \quad (\theta(S) - \theta(S^*)) \left( 1 - \frac{\Phi(S^*)}{\Phi(S)} \right) = 0$$

by (5.4), and thus  $S = S^*$  by assumption  $(B_1)$ . Furthermore,  $\dot{V} = 0$  implies that

$$(5.9) \quad \frac{g_j(S, I_j)}{g_j(S^*, I_j^*)} = \frac{\phi_{ij}(I_j)}{\phi_{ij}(I_j^*)} = \frac{\psi_j(I_j)}{\psi_j(I_j^*)} = \lambda, \quad i, j = 1, \dots, n,$$

using properties of  $s(x) = 1 - x + \ln x$  and strong connectivity of the weighted graph  $(G, M)$ . Along any solution that stays in the set where  $\dot{V} = 0$ , we necessarily have

$$S = S^*, \quad g_j(S, I_j) = \lambda g_j(S^*, I_j^*), \quad j = 1, \dots, n.$$

Substituting these relations into the first equation of (2.2), we obtain

$$0 = \theta(S^*) - \lambda \sum_{j=1}^n g_j(S^*, I_j^*).$$

Since the expression on the right-hand side is linear in  $\lambda$ , the equation holds only at  $\lambda = 1$ , namely at  $P^*$ . Letting  $\lambda = 1$  in (5.4) we know that

$$g_j(S, I_j) = g_j(S^*, I_j^*), \quad \sum_{i=1}^n \phi_{ij}(I_j) = \sum_{i=1}^n \phi_{ij}(I_j^*), \quad \psi_j(I_j) = \psi_j(I_j^*),$$

and it follows from monotonicity assumption  $(B_4)$  that  $I_j = I_j^*$ ,  $j = 1, \dots, n$ . Therefore, the only invariant set in the set  $\{\dot{V} = 0\}$  is the singleton  $\{P^*\}$ . By LaSalle’s invariance principle,  $P^*$  is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ . As a consequence,  $P^*$  is also unique.  $\square$

Assumptions  $(B_1)$ – $(B_4)$  are more general and more flexible than earlier conditions on nonlinear incidences. For instance, if the nonlinear incidence  $g_i(S, I_i)$  takes the separable form  $g_i(S, I_i) = p(S)q_i(I_i)$  and if  $p(S)$  is strictly increasing, then we can take  $\Phi(S) = p(S)$  in assumption  $(B_2)$  and obtain the following assumption for function  $q_i(I_i)$ :

$$(5.10) \quad (q_i(I_i) - q_i(I_i^*)) \left( \frac{q_i(I_i)}{\psi(I_i)} - \frac{q_i(I_i^*)}{\psi(I_i^*)} \right) \leq 0, \quad I_i \neq I_i^*.$$

Apart from difference in notations, this condition is the same as condition (5.1) in [13]. Furthermore, if  $\psi_i(I_i) = \delta_i I_i$ , then condition (5.10) becomes

$$(5.11) \quad (q_i(I_i) - q_i(I_i^*)) \left( \frac{q_i(I_i)}{I_i} - \frac{q_i(I_i^*)}{I_i^*} \right) \leq 0, \quad I_i \neq I_i^*.$$

A sufficient condition for (5.11) is that if  $q_i(I_i)$  is monotonically increasing and concave down, which is satisfied by classes of nonlinear functions

$$q_i(I_i) = I_i^{p_i} \quad \text{and} \quad q_i(I_i) = \frac{I_i^{p_i}}{1 + \kappa_i I_i^{p_i}}, \quad 0 < p_i \leq 1, \kappa_i \geq 0,$$

commonly used in the literature of epidemic modeling. We also remark that, when  $g_i(S, I_i) = p(S)q_i(I_i)$  and  $\theta(S) = \Lambda - dS$ , if  $p(S)$  is strictly increasing, then assumption  $(B_1)$  is automatically satisfied. In this case, conditions like (5.10) are subjected only on  $q_i(I_i)$ , not on  $p(S)$ .

**6. Two special cases.** To illustrate our main results in sections 4 and 5, we consider two special cases. Throughout the section, we assume that  $f(N) \equiv 1$ .

**6.1. Separable incidence and linear transfer among compartments.** We assume that the nonlinear incidence is in separable form,  $g_j(S, I_j) = p(S)q_j(I_j)$ , and that transfer and mortality functions are linear,  $\phi_{ij}(I_j) = \tilde{\phi}_{ij}I_j$  and  $\zeta_i(I_i) = \tilde{\zeta}_iI_i$ , for  $1 \leq i, j \leq n$ . Then, system (2.6) becomes

$$(6.1) \quad \begin{aligned} S' &= \theta(S) - p(S) \sum_{j=1}^n q_j(I_j), \\ I_1' &= p(S) \sum_{j=1}^n q_j(I_j) + \sum_{j=1}^n \tilde{\phi}_{1j}I_j - \tilde{\psi}_1I_1, \\ I_i' &= \sum_{j=1}^n \tilde{\phi}_{ij}I_j - \tilde{\psi}_iI_i, \quad i = 2, 3, \dots, n, \end{aligned}$$

where  $\tilde{\psi}_i = \sum_{j=1}^{n+1} \tilde{\phi}_{ji} + \tilde{\zeta}_i$ ,  $i = 1, \dots, n$ .

With these special classes of functions, assumptions  $(H_1)$ – $(H_8)$  are reduced to the following:

- $(H'_1)$  There exists  $\bar{S} > 0$  such that  $\theta(\bar{S}) = 0$  and  $\theta(S)(S - \bar{S}) < 0$  for all  $S \geq 0$  and  $S \neq \bar{S}$ .
- $(H'_2)$  For  $1 \leq j \leq n$ ,  $q_j(I_j) \geq 0$  for all  $I_j \geq 0$ , and  $q_j(0) = 0$ ;  $p(S) \geq 0$  for  $S \geq 0$  and  $p(0) = 0$ .
- $(H'_3)$  For  $1 \leq i, j \leq n$ ,  $\tilde{\phi}_{ij} \geq 0$ , and  $\sum_{j=1}^n \tilde{\phi}_{ji} > 0$  for each  $i$ .
- $(H'_4)$  For  $1 \leq i \leq n$ ,  $\tilde{\zeta}_i > 0$ .
- $(H'_5)$  For  $1 \leq i \leq n$ , there exists  $\tilde{c}_i \geq 0$ , such that  $\lim_{I_i \rightarrow 0^+} \frac{q_i(I_i)}{I_i} = \tilde{c}_i$ , and  $\max_i \{\tilde{c}_i\} > 0$ .

It can be verified that functions of the form  $\theta(S) = \Lambda - dS + rS(1 - \frac{S}{K})$ ,  $q_i(I_i) = \beta_i I_i^{p_i}$  and  $q_i(I_i) = \frac{\beta_i I_i^{p_i}}{1 + \kappa_i I_i^{p_i}}$  satisfy assumptions  $(H'_1)$ – $(H'_5)$ . Furthermore, the basic reproduction number is given as

$$R_0 = \rho(E_1 B_1^{-1}),$$

where

$$E_1 = p(\bar{S}) \begin{pmatrix} \frac{\tilde{c}_1}{\tilde{\psi}_1} & \frac{\tilde{c}_2}{\tilde{\psi}_2} & \dots & \frac{\tilde{c}_n}{\tilde{\psi}_n} \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 0 \end{pmatrix}, \quad B_1 = \begin{pmatrix} 1 & -b_{12} & \dots & -b_{1n} \\ -b_{21} & 1 & \dots & -b_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -b_{n1} & -b_{n2} & \dots & 1 \end{pmatrix},$$

with  $b_{ij} = \frac{\tilde{\phi}_{ij}}{\psi_j}$ .

Assumptions  $(A_1)$  and  $(A_2)$  are now reduced to the following two assumptions.

$(A'_1)$  Function  $p(S)$  is monotonically increasing for  $0 \leq S \leq \bar{S}$ , and  $p(S) = p(\bar{S})$  if and only if  $S = \bar{S}$ .

$(A'_2)$  For  $1 \leq i \leq n$ ,  $\tilde{c}_i = \sup_{I_i > 0} \frac{q_i(I_i)}{I_i}$ .

Following Theorem 4.1 we have the following result.

**THEOREM 6.1.** *Suppose that assumptions  $(H'_1)$ – $(H'_5)$  hold. If  $R_0 \leq 1$  and assumptions  $(A'_1)$  and  $(A'_2)$  hold, then the disease-free equilibrium  $P_0$  is globally asymptotically stable in  $\Gamma$ .*

By choosing  $\Phi(S) = p(S)$ , assumptions  $(B_1)$ – $(B_4)$  reduce to the following two conditions.

$(B'_1)$  For  $S \neq S^*$ ,  $(S - S^*)(\theta(S) - \theta(S^*)) < 0$ .

$(B'_2)$  For  $0 \leq S \leq \bar{S}$ ,  $p(S)$  is strictly increasing; for  $I_j > 0, 1 \leq j \leq n$ ,

$$(q_j(I_j) - q_j(I_j^*)) \left( \frac{q_j(I_j)}{I_j} - \frac{q_j(I_j^*)}{I_j^*} \right) \leq 0.$$

As we commented at the end of section 5, condition  $(B'_2)$  is satisfied if  $q_j(I_j)$  is strictly increasing and concave down. Such properties are satisfied by functions of the forms  $q_j(I_j) = \beta_j I_j^{p_j}$  and  $q_j(I_j) = \frac{\beta_j I_j^{p_j}}{1 + \kappa_j I_j^{p_j}}$ , with  $0 < p_j \leq 1, \kappa_j \geq 0$ .

The weight matrix  $M = (m_{ij})$  in (5.1) becomes

$$(6.2) \quad m_{ij} = \begin{cases} \tilde{\phi}_{1j} I_j^* + p(S^*) q_j(I_j^*) & \text{if } i = 1, \\ \tilde{\phi}_{ij} I_j^* & \text{if } i \geq 2. \end{cases}$$

The following result follows from Theorem 5.1.

**THEOREM 6.2.** *Suppose that assumptions  $(H'_1)$ – $(H'_5)$  hold. Assume that matrix  $M$  defined in (6.2) is irreducible, and that assumptions  $(B'_1)$  and  $(B'_2)$  hold. Then, when  $R_0 > 1$ , there exists a unique endemic equilibrium  $P^*$  to system (6.1) and it is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ .*

**6.2. Bilinear incidence and nonlinear transfer among compartments.**

We consider bilinear incidence  $g_j(S, I_j) = \beta_j I_j S$ . System (2.6) becomes

$$(6.3) \quad \begin{aligned} S' &= \theta(S) - \sum_{j=1}^n \beta_j I_j S, \\ I'_1 &= \sum_{j=1}^n \beta_j I_j S + \sum_{j=1}^n \phi_{1j}(I_j) - \psi_1(I_1), \\ I'_i &= \sum_{j=1}^n \phi_{ij}(I_j) - \psi_i(I_i), \quad i = 2, 3, \dots, n. \end{aligned}$$

Assumptions  $(H_2)$  and  $(H_3)$  are automatically satisfied. Assumption  $(H_6)$  becomes the following:

$(H''_6)$  There exist constants  $0 \leq \tilde{c}_i \leq \infty, 1 \leq i \leq n$ , and  $\max_i \{\tilde{c}_i\} > 0$ , such that  $\lim_{I_i \rightarrow 0^+} \frac{I_i}{\psi_i(I_i)} = \tilde{c}_i$ .

The basic reproduction number  $R_0$  is defined as  $R_0 = \rho(E_2 B_2^{-1})$  with

$$E_2 = \begin{pmatrix} \beta_1 \bar{S} \bar{c}_1 & \beta_2 \bar{S} \bar{c}_2 & \cdots & \beta_n \bar{S} \bar{c}_n \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 1 & -b_{12} & \cdots & -b_{1n} \\ -b_{21} & 1 & \cdots & -b_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -b_{n1} & -b_{n2} & \cdots & 1 \end{pmatrix}.$$

Assumption  $(A_1)$  simplifies to

$$(A_1'') \text{ For } 1 \leq i \leq n, \quad \bar{c}_i = \sup \frac{I_i}{\psi_i(I_i)}.$$

Assumption  $(B_2)$  simplifies to (by choosing  $\Phi(S) = S$ )

$$(B_2'') (I_j - I_j^*) \left( \frac{I_j}{\psi_j(I_j)} - \frac{I_j^*}{\psi_j(I_j^*)} \right) \leq 0, \quad 1 \leq j \leq n.$$

We note that assumption  $(B_2'')$  holds if  $\psi_j$  is linear.

Then, with the bilinear incidence, assumptions  $(H_1)$ – $(H_7)$  are replaced by  $(H_1)$ ,  $(H_4)$ ,  $(H_5)$ , and  $(H_6'')$ ,  $(H_7)$ , and  $(H_8)$ . If  $R_0 \leq 1$ , then Theorem 4.1 holds under  $(A_1'')$  and  $(A_2)$ , while if  $R_0 > 1$ , Theorem 5.1 holds under assumptions  $(B_1)$ ,  $(B_2'')$ , and  $(B_3)$ .

**7. Summary and discussions.** In this paper, we have formulated a general class of multistage epidemic models with disease progression and amelioration. Among the new features is that individuals are allowed to move from one stage of the infection to any other stage either forward (progression) or backward (amelioration) with certain transfer rates. We have also incorporated general classes of nonlinear demographic functions for the host population, nonlinear incidence functions that are also density dependent, as well as nonlinear transfer and removal functions from each disease stage. Under biologically motivated conditions, we have derived the basic reproduction number  $R_0$  and proved that the global dynamics are completely determined by the value of  $R_0$ ; if  $R_0 \leq 1$ , then the disease-free equilibrium is globally asymptotically stable, and the disease always dies out from all stages. If  $R_0 > 1$ , then the disease persists in all stages. In the special case that the incidence is density-independent, we have proved that a unique endemic equilibrium  $P^*$  is globally asymptotically stable if  $R_0 > 1$ .

Our models contain many important classes of epidemic models with multiple stages and multiple compartments in the literature. Hyman, Li, and Stanley [22] formulated a class of staged progression (SP) models for the progression of HIV. Similar structures in the SP models have appeared in earlier works of Jacquez and his collaborators (see [24, 39]) on HIV/AIDS modelling. SP models are further extended to SP and amelioration models in McCluskey [14, 36], Guo and Li [15, 16], and in recent works of Sallet and his collaborators [2, 7, 23]. In these earlier models, transfer of individuals is to the adjacent stage either forward (disease progression) or backward (amelioration). As a result, the transfer matrix is tridiagonal. This allows explicit construction of global Lyapunov functions using matrix techniques. In our model, the transfer matrix is a full matrix, and previous construction of Lyapunov functions is not applicable. This makes the application of the graph-theoretic technique developed in our earlier work [17, 18, 31, 32] essential in our proof of the uniqueness and global stability of the endemic equilibrium. Our results in the present paper mark the first time that the graph-theoretic technique is shown to work for epidemic models with general discrete stage structures.

We have allowed infectivity at an infectious stage to be zero, so that these stages can be regarded as latent or quarantined. Our results and proof are applicable to



earlier models with multiple latent stages [2, 23] and epidemic models of SIQR type with quarantined compartment [20]. In the special case when  $n = 2$  and  $g_1 = 0$ , our model reduces to the well-known SEIR model. Our results and proof generalize those in [25, 26].

Nonlinear functions are used in our models to describe incidence, disease progression, disease amelioration, and host population demography. These nonlinear elements have been used in the literature, and the methods of Lyapunov functions have been used for models that incorporate some of these nonlinearities [13, 26, 45]; none of these earlier models have the degree of generality in our model.

One limitation in our model is that we have used exponential distributions for residence time for individuals in a compartment  $I_j$ . Further extension of the model can incorporate general distributions for disease progression or amelioration as discussed in [9, 10].

**Appendix. Some combinatorial identities.**

Given a weighted digraph  $\mathcal{G}$  with  $n$  vertices ( $n \geq 2$ ), define the weight matrix  $A = (a_{ij})_{n \times n}$  whose entry  $a_{ij}$  equals the weight of arc  $(j, i)$  if it exists, and 0 otherwise. For our purpose, we denote a weighted digraph as  $(\mathcal{G}, A)$ . The *Laplacian matrix* of  $(\mathcal{G}, A)$  is defined as

$$(A.1) \quad L = \begin{pmatrix} \sum_{k \neq 1} a_{1k} & -a_{12} & \cdots & -a_{1n} \\ -a_{21} & \sum_{k \neq 2} a_{2k} & \cdots & -a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -a_{n1} & -a_{n2} & \cdots & \sum_{k \neq n} a_{nk} \end{pmatrix}.$$

Let  $c_i$  denote the co-factor of the  $i$ th diagonal element of  $L$ . Then  $(c_1, \dots, c_n)^T$  is a right eigenvector of  $L$  with respect to the eigenvalue 0. The following result gives a graph-theoretic description of  $c_i$  and is customarily referred to as Kirchhoff’s matrix tree theorem. We refer the reader to [38] for its proof.

PROPOSITION A.1 (Kirchhoff’s matrix tree theorem). *Assume  $n \geq 2$ . Then*

$$(A.2) \quad c_i = \sum_{\mathcal{T} \in \mathbb{T}_i} w(\mathcal{T}), \quad i = 1, 2, \dots, n,$$

where  $\mathbb{T}_i$  is the set of all spanning trees  $\mathcal{T}$  of  $(\mathcal{G}, A)$  that are rooted at vertex  $i$ , and  $w(\mathcal{T})$  is the weight of  $\mathcal{T}$ . In particular, if  $(\mathcal{G}, A)$  is strongly connected, then  $c_i > 0$  for  $1 \leq i \leq n$ .

The following tree cycle identity was first proved in [32]. We refer the reader to [32] for its proof.

PROPOSITION A.2 (tree cycle identity). *Assume  $n \geq 2$ . Let  $c_i$  be given in Proposition A.1. Then the following identity holds:*

$$(A.3) \quad \sum_{i,j=1}^n c_i a_{ij} F_{ij}(x) = \sum_{\mathcal{Q} \in \mathcal{Q}} w(\mathcal{Q}) \sum_{(s,r) \in E(\mathcal{C}_{\mathcal{Q}})} F_{rs}(x).$$

Here  $F_{ij}(x), 1 \leq i, j \leq n, x \in \mathbb{R}^m$ , are arbitrary functions,  $\mathcal{Q}$  is the set of all spanning unicyclic graphs of  $(\mathcal{G}, A)$ ,  $w(\mathcal{Q})$  is the weight of  $\mathcal{Q}$ , and  $\mathcal{C}_{\mathcal{Q}}$  denotes the directed cycle of  $\mathcal{Q}$ .

The following identity was first established in [32] and follows directly from the tree cycle identity.

COROLLARY A.3. *Let  $c_i$  be given in Kirchhoff's matrix tree theorem, and let  $\{G_i(x_i)\}_{i=1}^n$  be any family of functions. Then the following identity holds:*

$$(A.4) \quad \sum_{i,j=1}^n c_i a_{ij} G_i(x_i) = \sum_{i,j=1}^n c_i a_{ij} G_j(x_j).$$

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