MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **6**, Number **2**, April **2009**

doi:10.3934/mbe.2009.6.321

pp. **321–332**

EPIDEMIC MODELS WITH DIFFERENTIAL SUSCEPTIBILITY AND STAGED PROGRESSION AND THEIR DYNAMICS

James M. Hyman

Theoretical Division, MS-B284, Center for Nonlinear Studies
Los Alamos National Laboratory, Los Alamos, NM 87545, USA

Jia Li

Department of Mathematical Sciences, University of Alabama in Huntsville
Huntsville, AL 35899, USA

In honor of the Birthdays of Professors Fred Brauer and Karl Hadeler

Abstract. We formulate and study epidemic models with differential susceptibilities and staged-progressions, based on systems of ordinary differential equations, for disease transmission where the susceptibility of susceptible individuals vary and the infective individuals progress the disease gradually through stages with different infectiousness in each stage. We consider the contact rates to be proportional to the total population or constant such that the infection rates have a bilinear or standard form, respectively. We derive explicit formulas for the reproductive number R_0, and show that the infection-free equilibrium is globally asymptotically stable if $R_0 < 1$ when the infection rate has a bilinear form. We investigate existence of the endemic equilibrium for the two cases and show that there exists a unique endemic equilibrium for the bilinear incidence, and at least one endemic equilibrium for the standard incidence when $R_0 > 1$.

1. **Introduction.** Variation of susceptible individuals, possibly caused by genetic factors, age, health, vaccination, or past exposure to the disease, many lead to their differentiation of susceptibility to infection. For example, the efficacy of available vaccinations for many infectious diseases is not perfect. Vaccinated individuals may still contract the disease and the susceptibility varies from individual to individual. Differential susceptibility of infection can occur after vaccination is administered for infectious diseases. Rubeola, more commonly known as the "red measles," is a highly contagious exanthematous viral illness. Prevention of disease is the most effective method of handling rubeola. Despite widespread vaccination programs, however, many women remain susceptible [16].

Implementation of the WHO guidelines for vaccination is universally recognized as one of the most efficient ways of preventing hepatitis B (HB) on a global scale. Vaccinated individuals impose life-threatening conditions on the virus. The induced

2000 *Mathematics Subject Classification.* 34D20, 34D23, 92D30.

Key words and phrases. differential susceptibility, staged progression, reproductive number, endemic equilibrium, global stability.

This research was supported partially by the Department of Energy (contract no. W-7405-ENG-36), by the Applied Mathematical Sciences program (no. KC-07-01-01), and by Jia Li's grant from the National Science Foundation (no. DMS-0412386).

Jia Li: the corresponding author.

anti-HBs is generally able to clear an invasion quickly and efficiently. However, if the virus produces mutants (vaccine escape mutants) that are not recognized by these antibodies and prevent them from eliminating the invaders, the vaccine is only partially effective. As a result, vaccinated individuals may still be differentially susceptible to the infection [6].

There is substantial biological evidence demonstrating that the presence of other sexually transmitted diseases (STDs) increases the likelihood of both transmitting and acquiring HIV. Individuals who are infected with other STDs are at least two to five times more likely than uninfected individuals to acquire HIV if they are exposed to the virus through sexual contact. In addition, if an HIV-infected individual is also infected with another STD, that person is more likely to transmit HIV through sexual contact than other HIV-infected persons [1, 19, 5].

Compartmental differential susceptibility (DS) susceptible-infective-removed (SIR) models were studied in [8] to gain insight into the transmission dynamics of diseases with differential susceptibility whereas it was assumed that the infectives are homogeneous such that there is one group of infectives. While this is true for some diseases, great variability in the infectiousness among infected individuals has also been shown in many studies of infectious diseases [10]. To include both variabilities of susceptibility and infectiousness, we formulate compartmental SIR models with differential susceptibility and staged progression (DSSP) in Section 2. We derive explicit formulas for the reproductive number R_0 using the method of next generation operator in Section 3. As the reproductive number $R_0 < 1$, we show that the infection-free equilibrium is not only locally, but also globally asymptotically stable for models with bilinear incidence by using a Liapunov function in Section 4. We also investigate existence of the endemic equilibrium whose components are all positive in Section 5. We discuss how the DSSP models can be applied to various situations in Section 6.

2. **The model formulation.** Suppose that an infectious disease spreads in a population consisting of susceptible, infective (exposed), and removed or recovered individuals. The susceptibles are divided into n groups based on their susceptibilities. A constant influx S^0 enters these susceptible groups and is distributed, based on the inherent susceptibilities of the individuals, in such a way that the input flow into group S_i is $p_i S^0$, with $\sum_{i=1}^{n} p_i = 1$. We assume that the infectives from susceptible group S_i progress through m infection staged-subgroups, $I_{i1}, I_{i2}, \cdots, I_{im}$, $i = 1, \cdots, n$, with different infection rates, such that the infected susceptible individuals enter the first subgroup I_{i1} and then gradually progress from subgroup I_{i1} finally to subgroup I_{im}. We formulate our models such that if exposed individuals need to be considered in the model, the first subgroup I_{i1} stands for them with zero infectivity. The model, shown in Figure 1, can be described by the system of differential equations

$$\begin{aligned}
\frac{dS_i}{dt} &= \mu_i(d_i S^0 - S_i) - \lambda_i S_i, \quad i = 1, \cdots, n,\\
\frac{dI_{i1}}{dt} &= \lambda_i S_i - (\mu_{i1} + \gamma_{i1}) I_{i1}, \quad i = 1, \cdots, n,\\
\frac{dI_{ij}}{dt} &= \gamma_{i,j-1} I_{i,j-1} - (\mu_{ij} + \gamma_{ij}) I_{ij}, \quad i = 1, \cdots, n, \quad j = 2, \cdots, m,\\
\frac{dR_i}{dt} &= \gamma_{im} I_{im} - \delta_i R_i,
\end{aligned} \tag{2.1}$$

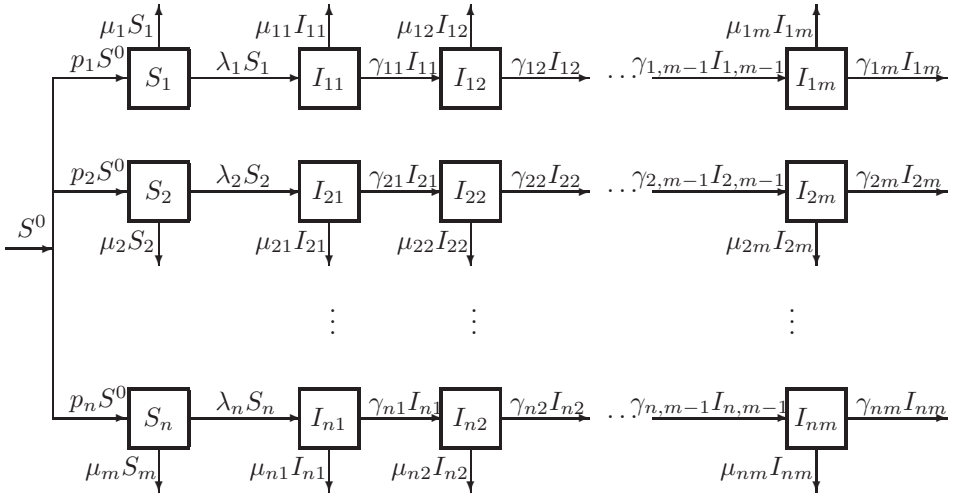

FIGURE 1. In this model, susceptible individuals are divided into n groups based on their susceptibilities. A constant influx S^0 is distributed into the n groups of susceptibles, based on their inherent susceptibility. After susceptibles in group i, $i = 1, \cdots, n$, are infected, they enter the infection group I_{i1} with infection rate λ_i, and progress through a series of stages where the progression rates γ_{ij} and infectivity β_{ij} vary. Since the transmissions caused by individuals in groups R_i are neglected, groups R_i are not shown in this schematic diagram.

where μ_i is the natural death rate for susceptible individuals in group i, μ_{ij} is the sum of the natural death rate and the disease-induced death rate for infected individuals in group i with infection stage j, λ_i is the rate of infection to susceptibles S_i, γ_{ij} is the average rate of progress from subgroup I_{ij} to subgroup $I_{i,j+1}$, for $j = 1, \cdots, m-1$, and γ_{im} is the rate at which infectives in subgroup I_{im} removed or recovered. We assume that the removed or recovered individuals, R_i, with the death rate δ_i, are no longer involved in the disease transmission or that their transmissions are negligible. We write $d_i = p_i/\mu_i$, $i = 1, \ldots, n$, for convenience.

The rate of infection, λ_i, is the rate at which a susceptible individual in group S_i gets infected and progresses to stage I_{i1}. It can be determined as

$$\lambda_i(t) = c(N)\alpha_i \sum_{k=1}^{n} \sum_{j=1}^{m} \beta_{kj} \frac{I_{kj}(t)}{N(t)},$$

where $c(N)$ is the average number of contacts per individual per unit of time that can be density-dependent, α_i is the susceptibility of the individuals in susceptible group S_i, β_{kj} is the infectivity of infectives in group I_{kj}, I_{kj}/N is the proportion of infectives in group I_{kj}, $N_k = S_k + \sum_{j=1}^{m} I_{kj}$ is the total number of individuals in group k active for the disease transmission, and $N = \sum_{k=1}^{n} N_k$ is the total number of active individuals involving the disease transmission.

If the contact rate is constant, denoted $c(N) := r$, the rate of infection has the standard form

$$\lambda_i(t) = r\alpha_i \sum_{k=1}^{n}\sum_{j=1}^{m} \beta_{kj} \frac{I_{kj}(t)}{N(t)}.$$

If the contact rate is proportional to the total active population N, such that $c(N) := cN$, the rate of infection has the bilinear form

$$\lambda_i(t) = c\alpha_i \sum_{k=1}^{n}\sum_{j=1}^{m} \beta_{kj} I_{kj}(t).$$

The rate of change of all the infectives in group i is

$$\frac{d}{dt}\sum_{j=1}^{m} I_{ij} = \lambda_i S_i - \sum_{j=1}^{m} \mu_{ij} I_{ij} - \gamma_{im} I_{im}, \quad i = 1, \cdots, n,$$

and the rate of change of the total population in group i satisfies

$$\frac{dN_i}{dt} = \mu_i \left(d_i S^0 - S_i\right) - \sum_{j=1}^{m} \mu_{ij} I_{ij} - \gamma_{im} I_{im} \le p_i S^0 - \widehat{\mu}_i N_i, \quad i = 1, \cdots, n,$$

where $\widehat{\mu}_i = \min_{j=1}^{m} \mu_{ij}$, $i = 1, \cdots, n$. Hence the set Ω defined by $\Omega := \left\{0 < N_i < S^0 \frac{p_i}{\widehat{\mu}_i},\ i = 1, \cdots, n\right\}$ is a global attractor for $N_i > 0$, $i = 1, \cdots, n$, and positively invariant for system (2.1) such that, if N_i initially satisfies $0 < N_i < S^0 \frac{p_i}{\widehat{\mu}_i}$, then it remains in this range. We restrict our investigation of the dynamics of system (2.1) in set Ω hereafter.

3. **The reproductive number.** System (2.1) has an infection-free equilibrium of which infective components are all zero and susceptible components are positive. Denote this infection-free equilibrium by E_0. The local stability of E_0 determines epidemic threshold conditions under which the number of infectives will either increase or decrease to zero as a small number of infectives introduced into a fully susceptible population. These threshold conditions are characterized by the reproductive number, denoted by R_0. The formula of R_0 can be determined by either investigating the eigenvalues of the linearized system about the infection-free equilibrium [7, 12, 17] or the next-generation operator method [3, 2, 18]. We derive an explicit formula for R_0 for the models with the standard incidence form as follows.

The Jacobian matrix at the infection-free equilibrium $E_0 = \left(S_1^0, S_2^0, \cdots, S_n^0, I_{11}^0, I_{21}^0, \cdots, I_{n1}^0, I_{12}^0, I_{22}^0, \cdots, I_{n2}^0, \cdots, I_{1m}^0, I_{2m}^0, \cdots, I_{nm}^0\right)$, where $S_i^0 = d_i S^0$, $I_{ij}^0 = 0$, $i = 1, \cdots, n$, $j = 1, \cdots, m$, has the form

$$\begin{pmatrix} J_{00} & 0 \\ 0 & J \end{pmatrix},$$

where $J_{00} = \operatorname{diag}(-\mu_1, \cdots, -\mu_n)$ and

$$J = \begin{pmatrix} P_{11} + J_{11} & P_{12} & P_{13} & \cdots & P_{1,m-1} & P_{1m} \\ J_{21} & J_{22} & 0 & \cdots & 0 & 0 \\ 0 & J_{32} & J_{33} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & J_{m,m-1} & J_{mm} \end{pmatrix}, \tag{3.1}$$

with $J_{jj} = \text{diag}(-\sigma_{1j}, \cdots, -\sigma_{nj})$, $j = 1, \cdots, m$, where $\sigma_{ij} := \mu_{ij} + \gamma_{ij}$, $J_{j,j-1} = \text{diag}(\gamma_{1,j-1}, \cdots, \gamma_{n,j-1})$, $j = 2, \cdots, m$, and

$$P_{1j} = \frac{r}{\overline{D}} \begin{pmatrix} \alpha_1 d_1 \beta_{1j} & \alpha_1 d_1 \beta_{2j} & \dots & \alpha_1 d_1 \beta_{nj} \\ \alpha_2 d_2 \beta_{1j} & \alpha_2 d_2 \beta_{2j} & \dots & \alpha_2 d_2 \beta_{nj} \\ \vdots & \vdots & \ddots & \vdots \\ \alpha_n d_n \beta_{1j} & \alpha_n d_n \beta_{2j} & \dots & \alpha_n d_n \beta_{nj} \end{pmatrix}, \quad j = 1, \cdots, m.$$

Here we write $\bar{D} := \sum_{l=1}^{n} d_l$.

The local stability of the infection-free equilibrium is determined by matrix J. Using the next generation operator method, we define matrices F and V by

$$F := \begin{pmatrix} P_{11} & P_{12} & P_{13} & \dots & P_{1m} \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 0 \end{pmatrix},$$

$$V := \begin{pmatrix} -J_{11} & 0 & 0 & \dots & 0 & 0 \\ -J_{21} & -J_{22} & 0 & \dots & 0 & 0 \\ 0 & -J_{32} & -J_{33} & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -J_{m-1,m-1} & 0 \\ 0 & 0 & 0 & \dots & -J_{m,m-1} & -J_{mm} \end{pmatrix}. \tag{3.2}$$

Then F is a nonnegative matrix and V is an M-matrix. The reproductive number R_0 equals the spectral radius of the next generation operator FV^{-1} [18]:

$$R_0 = \rho\left(FV^{-1}\right).$$

The inverse matrix V^{-1}, as shown in [9], is the lower triangular matrix given by

$$V^{-1} = \begin{pmatrix} V_{11} & 0 & \dots & 0 \\ V_{21} & V_{22} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ V_{m1} & V_{m2} & \cdots & V_{mm} \end{pmatrix}, \tag{3.3}$$

where

$$V_{ii} = -J_{ii}^{-1}, \qquad i = 1, \cdots, m,$$

and V_{ij} are defined recursively by

$$V_{ij} = -J_{i,i-1} V_{i-1,j} J_{ii}^{-1}, \qquad i = 2, \cdots, m, \quad j < i. \tag{3.4}$$

Since

$$FV^{-1} = \begin{pmatrix} \sum_{j=1}^{m} P_{1j} V_{j1} & \sum_{j=2}^{m} P_{1j} V_{j2} & \dots & P_{1m} V_{mm} \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{pmatrix},$$

we have

$$\rho\left(FV^{-1}\right) = \rho\left(\sum_{j=1}^{m} P_{1j} V_{j1}\right).$$

It follows from (3.4), iteratively, that

$$\begin{aligned} V_{j1} =& - J_{j,j-1}V_{j-1,1}J_{jj}^{-1} = J_{j,j-1}J_{j-1,j-2}V_{j-2,1}J_{j-1,j-1}^{-1}J_{jj}^{-1} = \cdots \\ =&(-1)^{j-1}\prod_{k=2}^{j} J_{k,k-1}V_{11}\prod_{k=2}^{j} J_{kk}^{-1} = (-1)^{j}\prod_{k=2}^{j} J_{k,k-1}\prod_{k=1}^{j} J_{kk}^{-1} \\ =&\text{diag}\left(\frac{\prod_{k=1}^{j-1}\gamma_{1k}}{\prod_{k=1}^{j}\sigma_{1k}},\cdots,\frac{\prod_{k=1}^{j-1}\gamma_{nk}}{\prod_{k=1}^{j}\sigma_{nk}}\right), \end{aligned} \tag{3.5}$$

for $j \geq 2$. Hence

$$\begin{aligned} \sum_{j=1}^{m} P_{1j}V_{j1} =& \sum_{j=1}^{m} P_{1j}\text{diag}\left(\frac{b_{1j}}{\sigma_{1j}},\cdots,\frac{b_{nj}}{\sigma_{nj}}\right) \\ =&\frac{r}{\bar{D}}\sum_{j=1}^{m}\begin{pmatrix} \alpha_1 d_1\dfrac{\beta_{1j}b_{1j}}{\sigma_{1j}} & \alpha_1 d_1\dfrac{\beta_{2j}b_{2j}}{\sigma_{2j}} & \dots & \alpha_1 d_1\dfrac{\beta_{nj}b_{nj}}{\sigma_{nj}} \\ \alpha_2 d_2\dfrac{\beta_{1j}b_{1j}}{\sigma_{1j}} & \alpha_2 d_2\dfrac{\beta_{2j}b_{2j}}{\sigma_{2j}} & \dots & \alpha_2 d_2\dfrac{\beta_{nj}b_{nj}}{\sigma_{nj}} \\ \vdots & \vdots & \ddots & \vdots \\ \alpha_n d_n\dfrac{\beta_{1j}b_{1j}}{\sigma_{1j}} & \alpha_n d_n\dfrac{\beta_{2j}b_{2j}}{\sigma_{2j}} & \dots & \alpha_n d_n\dfrac{\beta_{nj}b_{nj}}{\sigma_{nj}} \end{pmatrix}, \end{aligned}$$

where

$$b_{ij} := \prod_{k=1}^{j-1}\frac{\gamma_{ik}}{\mu_{ik}+\gamma_{ik}}, \quad j = 1,\cdots,m,$$

and $\prod_{k=1}^{0}\cdot = 1$ by convention.

Note that

$$\sum_{j=1}^{m} P_{1j}V_{j1} = \frac{r}{\bar{D}}D_1\begin{pmatrix} 1 & 1 & \dots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \dots & 1 \end{pmatrix}\sum_{j=1}^{m} D_{2j},$$

where $D_1 := \text{diag}\,(\alpha_1 d_1,\cdots,\alpha_n d_n)$ and $D_{2j} := \text{diag}\left(\dfrac{\beta_{1j}b_{1j}}{\sigma_{1j}},\cdots,\dfrac{\beta_{nj}b_{nj}}{\sigma_{nj}}\right)$. Then the rank of $\sum_{j=1}^{m} P_{1j}V_{j1}$ is one, and hence the spectral radius of $\sum_{j=1}^{m} P_{1j}V_{j1}$ equals its trace. Therefore the reproductive number for system (2.1) has the explicit formula

$$R_0 = \frac{r}{\bar{D}}\sum_{j=1}^{m}\sum_{i=1}^{n}\frac{\alpha_i d_i \beta_{ij} b_{ij}}{\sigma_{ij}} = r\sum_{i=1}^{n}\frac{d_i\alpha_i}{\bar{D}}\sum_{j=1}^{m}\frac{\beta_{ij}b_{ij}}{\sigma_{ij}}. \tag{3.6}$$

Theorem 3.1. *Let the reproductive number R_0 be defined as in (3.6). Then if $R_0 < 1$ the infection-free equilibrium E_0 is locally asymptotically stable, and if $R_0 > 1$ the infection-free equilibrium E_0 is unstable.*

The mean duration of infection in group i is

$$\bar{\tau_i} := \sum_{j=1}^{m}\frac{b_{ij}}{\sigma_{ij}} = \sum_{j=1}^{m}\frac{b_{ij}}{\mu_{ij}+\gamma_{ij}}.$$

If we define the mean transmissibility for group i as

$$\bar{\beta}_i := \frac{\alpha_i}{\bar{\tau}_i} \sum_{j=1}^{m} \frac{\beta_{ij} b_{ij}}{\mu_{ij} + \gamma_{ij}},$$

and the reproductive number for group i by

$$R_{0i} := r\bar{\beta}_i \bar{\tau}_i, \qquad i = 1, 2, \cdots, n,$$

then the reproductive number for the entire population is a weighted average of the reproductive numbers for these groups such that

$$R_0 = \sum_{i=1}^{n} \frac{d_i}{\overline{D}} R_{0i}.$$

It is similar to derive a formula of R_0 for the models with bilinear incidence form as

$$R_0^b = cS^0 \sum_{i=1}^{n} \alpha_i d_i \sum_{j=1}^{m} \frac{\beta_{ij} b_{ij}}{\sigma_{ij}} = S^0 \sum_{i=1}^{n} d_i R_{0i}.$$

4. **Global stability of the infection-free equilibrium.** We show that if $R_0 < 1$, the infection-free equilibrium is not only locally but also globally asymptotically stable for models with the bilinear incidence form.

Let $\mathbf{S} := (S_1, \cdots, S_n)^T$, $\mathbf{I} := (I_{11}, I_{12}, \cdots, I_{1m}, \cdots, I_{n1}, I_{n2}, \cdots, I_{nm})^T$. We can then write the infection rate λ_i as

$$\lambda_i = c\alpha_i \mathbf{UBI},$$

where

$$\mathbf{B} := \begin{pmatrix} \beta_{11} & \dots & \beta_{1m} & 0 & \dots & 0 & \dots & 0 & \dots & 0 \\ 0 & \dots & 0 & \beta_{21} & \dots & \beta_{2m} & \dots & 0 & \dots & 0 \\ & \vdots & & & \vdots & & \ddots & & \vdots & \\ 0 & \dots & 0 & 0 & \dots & 0 & \dots & \beta_{n1} & \dots & \beta_{nm} \end{pmatrix} \in \mathbb{R}^{n \times nm},$$

and $\mathbf{U} := (1, 1, \cdots, 1) \in \mathbb{R}^{1 \times n}$.

Define matrices

$$L_i := \begin{pmatrix} \sigma_{i1} & 0 & \dots & 0 & 0 \\ -\gamma_{i1} & \sigma_{i2} & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & \sigma_{i,m-1} & 0 \\ 0 & 0 & \dots & -\gamma_{i,m-1} & \sigma_{im} \end{pmatrix} \in \mathbb{R}^{m \times m}, \quad i = 1, \cdots, n,$$

$L := \operatorname{diag}(L_1, L_2, \cdots, L_n)$, and

$$\mathbf{P} := (r\alpha_1 S_1, 0, \cdots, 0, r\alpha_2 S_2, 0, \cdots, 0, r\alpha_n S_n, 0, \cdots, 0)^T \in \mathbb{R}^{nm \times 1},$$

such that

$$\mathbf{F} := (\lambda_1 S_1, 0, \cdots, 0, \lambda_2 S_2, 0, \cdots, 0, \lambda_n S_n, 0, \cdots, 0)^T = \mathbf{PUBI}.$$

Then the infective components of system (2.1) satisfy the system

$$\frac{d\mathbf{I}}{dt} = -L\mathbf{I} + \mathbf{F} = -L\mathbf{I} + \mathbf{PUBI}.$$

Let

$$C := (c_{11}, c_{12}, \cdots, c_{1m}, \cdots, c_{n1}, c_{n2}, \cdots, c_{nm}) = \mathbf{UB}L^{-1}.$$

Then $C > 0$ is a positive vector. We consider the Liapunov function

$$V = C\mathbf{I},$$

which is positive definite for $\mathbf{I} > 0$. The derivative of V along the system (2.1) equals

$$\begin{aligned}\left.\frac{dV}{dt}\right|_{(2.1)} &= -CL\mathbf{I} + C\mathbf{PUBI} = -\mathbf{UBI} + \mathbf{UB}L^{-1}\mathbf{PUBI} \\ &= \left(\mathbf{UB}L^{-1}\mathbf{P} - 1\right)\mathbf{UBI}.\end{aligned}$$

It follows from (3.3), (3.4), and (3.5) that

$$L_i^{-1}\mathbf{P} = \left(c\alpha_1 S_1 a_{11}^{\{1\}}, \cdots, c\alpha_1 S_1 a_{m1}^{\{1\}}, \cdots, c\alpha_n S_n a_{11}^{\{n\}}, \cdots, c\alpha_1 S_1 a_{m1}^{\{n\}}\right)^T,$$

where

$$a_{j1}^{\{i\}} = \frac{\prod_{k=1}^{j-1}\gamma_{ik}}{\prod_{k=1}^{j}\sigma_{ik}}, \quad i = 1, \cdots, n, \quad j = 1, \cdots, m.$$

Then

$$\mathbf{UB}L^{-1}\mathbf{P} = c\sum_{i=1}^{n}\alpha_i S_i \sum_{j=1}^{m} a_{j1}^{\{i\}}\beta_{ij}.$$

It follows from (2.1) that

$$S_i \le d_i S^0 + S_i(0)e^{-\mu_i t}.$$

Hence

$$\mathbf{UB}L^{-1}\mathbf{P} \le cS^0\sum_{i=1}^{n}\alpha_i d_i \sum_{j=1}^{m} a_{j1}^{\{i\}}\beta_{ij} + \varepsilon_1(t) = R_0 + \varepsilon_1(t),$$

where $\lim_{t\to\infty}\varepsilon_1(t) = 0$.

If $R_0 < 1$, then

$$\frac{dV}{dt} = \left(\mathbf{UB}L^{-1}\mathbf{P} - 1\right)\mathbf{UBI} \le (R_0 - 1)\mathbf{UBI} + \varepsilon_2(t) \le 0,$$

where $\lim_{t\to\infty}\varepsilon_2(t) = 0$. Notice that $\dfrac{dV}{dt} = 0$ only if $\mathbf{I} = \mathbf{0}$, in set Ω, if $R_0 < 1$. Therefore the infection-free equilibrium is globally asymptotically stable.

5. **Endemic equilibrium.** As the infection-free equilibrium becomes unstable and the disease spreads in the population, there possibly exists an endemic equilibrium with all components positive. We explore its existence for model (2.1) as follows.

The components of an endemic equilibrium for (2.1) must satisfy

$$\mu_i(d_i S^0 - S_i) = \lambda_i S_i, \tag{5.1a}$$

$$\lambda_i S_i = (\mu_{i1} + \gamma_{i1})I_{i1}, \tag{5.1b}$$

$$\gamma_{i,j-1}I_{i,j-1} = (\mu_{ij} + \gamma_{ij})I_{ij}, \quad j = 2, \cdots, m. \tag{5.1c}$$

For models with the bilinear incidence, we let $W := c\sum_{i=1}^{n}\sum_{j=1}^{m}\beta_{ij}I_{ij}$. Then $\lambda_i = W\alpha_i$.

Solving (5.1a) for S_i, we have

$$S_i = \frac{\mu_i d_i S^0}{\mu_i + \alpha_i W}, \quad i = 1, \cdots, n. \tag{5.2}$$

Substituting (5.2) into (5.1b) and solving for I_{i1}, we have

$$I_{i1} = \frac{\mu_{i1}\alpha_i d_i S^0 W}{\sigma_{i1}(\mu_{i1} + \alpha_i W)}, \quad i = 1, \cdots, n. \tag{5.3}$$

Solving (5.1c) recursively, we have

$$I_{ij} = \frac{\gamma_{i,j-1}\gamma_{i,j-2}\cdots\gamma_{i1}}{\sigma_{ij}\sigma_{i,j-1}\cdots\sigma_{i2}} I_{i1} = \frac{\sigma_{i1}}{\sigma_{ij}} b_{ij} I_{i1} = \sigma_{i1}\Delta_{ij} I_{i1}, \quad i = 1, \cdots, n, \quad j = 2, \cdots, m, \tag{5.4}$$

where $\Delta_{ij} := b_{ij}/\sigma_{ij}$. Notice $\Delta_{i1} = 1/\sigma_{i1}$. Then substituting (5.3) into (5.4), we have

$$I_{ij} = \frac{\mu_i \alpha_i d_i S^0 \Delta_{ij} W}{\mu_i + \alpha_i W}, \quad i = 1, \cdots, n, \quad j = 1, \cdots, m. \tag{5.5}$$

Substituting (5.2), (5.3), and (5.5) into W yields

$$W = c \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{\beta_{ij}\mu_i \alpha_i d_i S^0 \Delta_{ij} W}{\mu_i + \alpha_i W}.$$

Define function

$$G(W) := c \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{\beta_{ij}\mu_i \alpha_i d_i S^0 \Delta_{ij}}{\mu_i + \alpha_i W} - 1.$$

Note that $\lim_{W\to\infty} G(W) = -1$, $G(0) = R_0 - 1$, and

$$G'(W) = -c \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{\beta_{ij}\mu_i (\alpha_i)^2 d_i S^0 \Delta_{ij}}{(\mu_i + \alpha_i W)^2} < 0.$$

Then, if $R_0 < 1$ there exists no endemic equilibrium, and if $R_0 > 1$ there exists a unique endemic equilibrium for model (2.1).

For models with the standard incidence, we let $W := r \sum_{i=1}^{n} \sum_{j=1}^{m} \beta_{ij} I_{ij}/N$ without confusion. Then $\lambda_i = W\alpha_i$.

Solutions for S_i and I_{ij} have the same formulas as in (5.2) and (5.5). Then substituting them into W, we obtain

$$W \left(\sum_{i=1}^{n} \frac{\mu_i d_i S^0}{\mu_i + \alpha_i W} + \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{\mu_i \alpha_i d_i S^0 \Delta_{ij} W}{\mu_i + \alpha_i W} \right) = r \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{\beta_{ij}\mu_i \alpha_i d_i S^0 \Delta_{ij} W}{\mu_i + \alpha_i W}.$$

Define function

$$\begin{aligned} Q(W) :=& \sum_{i=1}^{n} \frac{\mu_i d_i S^0}{\mu_i + \alpha_i W} + \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{\mu_i \alpha_i d_i S^0 \Delta_{ij} W}{\mu_i + \alpha_i W} - r \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{\beta_{ij}\mu_i \alpha_i d_i S^0 \Delta_{ij}}{\mu_i + \alpha_i W} \\ =& S^0 \sum_{i=1}^{n} \frac{\mu_i d_i}{\mu_i + \alpha_i W} \left(1 + \alpha_i \sum_{j=1}^{m} (W - r\beta_{ij}) \Delta_{ij} \right). \end{aligned}$$

We have

$$\lim_{W\to\infty} Q(W) = S^0 \sum_{i=1}^{n} \mu_i d_i \sum_{j=1}^{m} \Delta_{ij} > 0,$$

and

$$Q(0) = S^0 \sum_{i=1}^{n} d_i \left(1 - r\alpha_i \sum_{j=1}^{m} \beta_{ij}\Delta_{ij}\right) = S^0 \bar{D}\,(1 - R_0)\,.$$

Then if $R_0 > 1$ there exists at least one positive W such that $Q(W) = 0$. That is, there exists at least one endemic equilibrium for model (2.1).

Moreover, it follows from

$$\begin{aligned} Q'(W) &= S^0 \sum_{i=1}^{n} \frac{\mu_i d_i \alpha_i}{(\mu_i + \alpha_i W)^2} \left(\sum_{j=1}^{m} \mu_i \Delta_{ij} + r\alpha_i \sum_{j=1}^{m} \beta_{ij}\Delta_{ij} - 1\right) \\ &= S^0 \sum_{i=1}^{n} \frac{\mu_i d_i \alpha_i}{(\mu_i + \alpha_i W)^2} \left(\sum_{j=1}^{m} \mu_i \Delta_{ij} + R_{0i} - 1\right), \end{aligned}$$

that if $\sum_{j=1}^{m} \mu_i \Delta_{ij} + R_{0i} > 1$, especially if $R_{0i} > 1$, for all $i = 1, \cdots, m$, then the endemic equilibrium is unique.

In summary, we have

Theorem 5.1. *If the infection rate has the bilinear form for model (2.1), then there exists no endemic equilibrium provided $R_0 < 1$, and a unique endemic equilibrium provided $R_0 > 1$. If the infection rate has the standard form for model (2.1), then there exists at least one endemic equilibrium provided $R_0 > 1$.*

6. **Concluding remarks.** We have formulated the compartmental differential susceptibility and staged-progression DSSP epidemic models with either the standard or bilinear incidence. The models are a combination of the DS and the SP models, which have been studied intensively but separately.

We derived explicit formulas for the reproductive number R_0 for the models with either the standard or the bilinear incidence, using the next generation operator method. The explicit formulas of R_0 for the models well fit in the calculations of R_0 for a variety of epidemiological models in the literature [7, 2, 13, 4]. That is, the reproductive number for each subgroup, R_{0i}, is defined as a product of the mean number of contacts, the mean infectivity, and the mean duration of infection, and then the reproductive number for the entire population, R_0, is defined as a weighted average of those R_{0i}.

For the models with the bilinear incidence, we showed that the infection-free equilibrium is not only locally but also globally asymptotically stable when $R_0 < 1$ by using a Liapunov function. We also showed that for these models, if $R_0 < 1$ there exists no endemic equilibrium, and if $R_0 > 1$ there exists a unique endemic equilibrium. Therefore, we exclude the possibility of the backward bifurcation. For the models with the standard incidence, we showed that if $R_0 > 1$ there exists at least one endemic equilibrium.

The DSSP model formulated in this paper can be applied to modeling of various disease transmissions. For example, suppose that HIV/AIDS spreads in a population with two groups, one of which consists of individuals who are infected with other STDs and one of which consists of individuals who are free of STDs before first engaging in sexual activities. As shown in [1, 19, 5], the presence of other STDs increases the likelihood of both transmitting and acquiring HIV. Individuals who

are infected with other STDs are at least two to five times more likely than uninfected individuals to acquire HIV, and if an HIV-infected individual is also infected with another STD, that person is more likely to transmit HIV through sexual contact than other HIV-infected persons. We denote the two groups as group 1 and 2, respectively, and assume that all infectives go through 4 infection stages: an early, highly infectious pre-antibody phase, two chronic stages at low infectivities, and a final stage at higher infectiousness [10, 14, 11, 15].

Let $\alpha_1 > \alpha_2$ and $\beta_{1j} > \beta_{2j}$, $j = 1, \cdots, 4$, be the corresponding susceptibilities and infectivities. Then the reproductive number of infection is given by

$$R_0 = \frac{d_1 R_{01} + d_2 R_{02}}{d_1 + d_2} = \frac{p\mu_2 R_{01} + (1-p)\mu_1 R_{02}}{p\mu_2 + (1-p)\mu_1}, \tag{6.1}$$

where

$$R_{0i} = r\alpha_i \sum_{j=1}^{4} \frac{\beta_{ij}}{\mu_{ij} + \gamma_{ij}} \prod_{k=1}^{4} \frac{\gamma_{ik}}{\mu_{ik} + \gamma_{ik}}, \quad i = 1, 2,$$

are the reproductive numbers for the two groups, and p is the fraction of the input flow of susceptibles into the group of individuals with infection of other STDs.

Based on the formula of the reproductive number in (6.1), it is clear that a strategy to reduce the infection is to decrease the reproductive number for each group, in particular, for the group with the cofactor of other STDs. Meanwhile, it can help bring the transmission under control if the distribution of the input flow into group 1 is reduced which implies that more routinely screening for STDs should be advised for preventing the transmission of HIV/AIDS.

Due to the fact that the efficacy of available vaccinations for many infectious diseases is not perfect. Vaccinated individuals may still contract the disease and their susceptibility varies from individual to individual. To model such a situation, we can divide a population into two groups, one of which has all vaccinated individuals and one of which has all unvaccinated individuals. The infectives may progress the disease through several infection stages. Model (2.1) can be applied and the explicit formulas for the reproductive number can provide helpful guidance for the strategies of control and prevention for the disease.

REFERENCES

[1] CDC Fact Sheet – The Role of STD Detection and Treatment in HIV Prevention, http://www.cdc.gov/std/hiv/STDFact-STD\&HIV.htm.

[2] O. Diekmann and J. A. P. Heesterbeek, "Mathematical Epidemiology of Infectious Diseases," Model building, analysis and interpretation. Wiley Series in Mathematical and Computational Biology. John Wiley & Sons, Ltd., Chichester, 2000.

[3] O. Diekmann, J. A. P. Heesterbeek and J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol., **28** (1990), 365–382.

[4] K. Dietz, J. A. P. Heesterbeek and D. W. Tudor, *The basic reproduction ratio for sexually transmitted diseases, Part 2. effects of variable HIV infectivity*, Math. Biosci., **117** (1993), 35–47.

[5] D. T. Fleming and J. N. Wasserheit, *From epidemiological synergy to public health policy and practice: The contribution of other sexually transmitted diseases to sexual transmission of HIV infection*, Sexually Transmitted Infections, **75** (1999), 3–17.

[6] G. Francois, M. Kew, P. Van Damme, M. J. Mphahlele and A. Meheus, *Mutant hepatitis B viruses: A matter of academic interest only or a problem with far-reaching implications*, Vaccine, **19** (2001), 3799–3815.

[7] J. M. Hyman and Jia Li, *An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations*, Math. Biosci., **167** (2000), 65–86.

[8] J. M. Hyman and Jia Li, *Differential susceptibility epidemic models*, J. Math. Biol., **50** (2005), 626–644.
[9] J. M. Hyman and Jia Li, *The reproductive number for an HIV model with differential infectivity and staged progression*, Linear Algebra and its Applications, **398** (2005), 101–116.
[10] J. M. Hyman, Jia Li and E. A. Stanley, *The differentiated infectivity and staged progression models for the transmission of HIV*, Math. Biosci., **155** (1999), 77–109.
[11] J. A. Jacquez, J. S. Koopman, C. P. Simon and I. M. Longini, *Role of the primary infection in epidemics of HIV infection in gay cohorts*, J. AIDS, **7** (1994), 1169–1184.
[12] Xiaodong Lin, *Qualitative analysis of an HIV transmission model*, Math. Biosci., **104** (1991), 111–134.
[13] R. M. May and R. M. Anderson, *Transmission dynamics of HIV infection*, Nature, **326** (1987), 137–142.
[14] M. Piatak, M. S. Saag, L. C. Yang, S. J. Clark, J. C. Kappes, K. C. Luk, B. H. Hahn, G. M. Shaw and J. D. Lifson, *High levels of HIV-1 in plasma during all stages of Infection determined by competitive PCR*, Science, **259** (1993), 1749–1754.
[15] T. C. Quinn, *Acute primary HIV infection*, JAMA, **278** (1997), 58–62.
[16] C. Signore, *Rubeola*, Primary Care Update for Ob/Gyns, **8** (2001), 138–140.
[17] C. P. Simon and J. A. Jacquez, *Reproduction numbers and the stability of equilibria of SI models for heterogeneous populations*, SIAM J. Appl. Math., **52** (1992), 541–576.
[18] P. van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci., **180** (2002), 29–48.
[19] J. N. Wasserheit, *Epidemiologic synergy: Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases*, Sexually Transmitted Diseases, **9** (1992), 61–77.

Received December 3, 2007. Accepted July 9, 2008.

E-mail address: hyman@lanl.gov
E-mail address: li@math.uah.edu