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Differential susceptibility epidemic models

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Abstract. We formulate compartmental differential susceptibility (DS) susceptible-infective-removed (SIR) models by dividing the susceptible population into multiple subgroups according to the susceptibility of individuals in each group. We analyze the impact of disease-induced mortality in the situations where the number of contacts per individual is either constant or proportional to the total population. We derive an explicit formula for the reproductive number of infection for each model by investigating the local stability of the infection-free equilibrium. We further prove that the infection-free equilibrium of each model is globally asymptotically stable by qualitative analysis of the dynamics of the model system and by utilizing an appropriately chosen Liapunov function. We show that if the reproductive number is greater than one, then there exists a unique endemic equilibrium for all of the DS models studied in this paper. We prove that the endemic equilibrium is locally asymptotically stable for the models with no disease-induced mortality and the models with contact numbers proportional to the total population. We also provide sufficient conditions for the stability of the endemic equilibrium for other situations. We briefly discuss applications of the DS models to optimal vaccine strategies and the connections between the DS models and predator-prey models with multiple prey populations or host-parasitic interaction models with multiple hosts are also given.

1. Introduction

Genetic variation of susceptible individuals many lead to their differentiation of susceptibility on infection. 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,

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however, many women remain susceptible such that two doses of live-attenuated vaccine should be administered for prevention [1].

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 anti-HB 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 [2].

Through their surface expression of CD38, $CD4^+$ T cells have shown differential susceptibility to M- and T-tropic HIV-1 infection. The $CD4^+CD38^-$ and $CD4^+CD45RA^-$ subsets have higher susceptibility to infection with the M-tropic Ba-L strain of HIV-1, and the $CD4^+CD38^+$ subset has higher susceptibility to infection with the T-tropic (LAI) strain of HIV-1 [3]. For the spread of Chagas disease, uninfected individuals are found in all reported studies of endemic areas and more than half of the variation in seropositivity is attributable to genetic factors, which influences the differential out-comes of T. cruzi infection [4,5]. Epidemiological data show a strong correlation between VT1 and VT2, produced by Verotoxin-producing Escherichia coli (VTEC), and the development of hemolytic-uremic syndrome (HUS). However, it is well recognized that not all patients who have VTEC-associated enterocolitis develop HUS even through the nature of the underlying host susceptibility is not understood [6,7].

There have been studies on variable infectivities [8–10], but few models are on the importance of variable susceptibility. While the model in [11] includes variable susceptibility, it is in terms of cellular automata and on a lattice. Effects of a variation in susceptibility to measles, smallpox, and whooping cough epidemics, have been studied in [12–14], by including periodic variations in susceptibility for simple SIR or SEIR (susceptible-exposed-infective-removed) models with a single equation for the susceptible individuals. Because of the periodic variations, the models become time-dependent and mathematically intractable.

To gain insight into the transmission dynamics of diseases with differential susceptibility, we propose compartmental DS models in a general setting. We start with a general DS model based on an SIR model, where infectives are either completely removed or isolated, or they have full immunity after they are recovered. We assume the susceptible individuals have variable susceptibility such that the susceptible population is divided into n groups based on their susceptibilities. The dynamics of the model are governed by a system of ordinary differential equations.

For the case when there is no disease-induced mortality such that the incidence of infection is bilinear, we derive the reproductive number from the local stability analysis of the infection-free equilibrium and prove that this infection-free equilibrium is globally asymptotically stable. When the reproductive number is greater than one, we show that there exists a unique endemic equilibrium and it is globally asymptotically stable by using a Liapunov function. We then study a DS model with disease-induced mortality. The incidence of infection is no longer bilinear, but standard [15]. We again obtain an explicit formula of the reproductive number

and show that the infection-free equilibrium is globally asymptotically stable if the reproductive number is less than one. If the reproductive number is greater than one, we show that there exists a unique endemic equilibrium, and provide stability conditions for the endemic equilibrium.

Finally, we give brief discussions of the transmission dynamics, based on our DS models. We point out that the DI models can be applied to determining optimal vaccination strategies and to predator-prey interactions with one predator and multiple prey species or to host-parasite interactions in special cases.

2. General model formulation

Suppose that an infectious disease spreads in a population. Our main interest is to investigate transmission dynamics of the disease. Hence we neglect demographic effects in the population and assume that the population approaches a steady state, S^0, if there is no disease infection and all individuals are susceptible. We suppose that infected individuals become fully immune or removed after they are recovered from the infection. Then, the transmission dynamics of the infection are assumed to be of an SIR type. A simple classical SIR model that describes the transmission dynamics of such infection consists of the following system of ordinary differential equations

$$\begin{cases} \dfrac{dS}{dt} = \mu(S^0 - S) - \lambda S, \\ \dfrac{dI}{dt} = \lambda S - (\mu + \gamma + \delta)I, \\ \dfrac{dR}{dt} = \gamma I - (\mu + \xi)R, \end{cases}$$

where S, I, and R denote the susceptibles, infectives, and recovered or removed individuals; μ is the natural death rate; μS^0 is a constant influx or recruitment rate; γ is the rate at which infectives are removed or become immune; and δ and ξ are the disease-induced mortality rates for the infectives and removed individuals, respectively.

The infectivity rate or the infection incidence λ is given by

$$\lambda = \alpha\beta c\frac{I}{N},$$

where α is the susceptibility of susceptible individuals, β is the infectious rate of infected individuals, $c = c(N)$ is the average number of contacts per individual, and I/N is the probability that a random contact is infectious, with $N = S + I + R$, the total population size.

To study the transmission dynamics due to differential susceptibility, we assume that the susceptible population is further divided into n groups, $S_1, S_2, \ldots, S_n$, such that individuals in each group have homogeneous susceptibility, but the susceptibilities of individuals from different groups are distinct. We let the influx be distributed into the n subgroups of susceptibles, based on their inherent susceptibility, in such

a way that the input flow into group S_i is $p_i \mu S^0$ with $\sum_{i=1}^{n} p_i = 1$. We then assume that the susceptible individuals stay in those groups until they become infected.

For model simplification, we assume homogeneous infectiousness of infected individuals so that they are aggregated into one group of infected individuals, I. We assume full immunity of recovered individuals such that these individuals are no longer susceptible after they recovered, or complete isolations after individuals are infected and diagnosed. This model is illustrated in Fig. 2.1 and the transmission dynamics of infection are governed by the more refined system of differential equations (2.1):

$$\begin{cases} \dfrac{dS_i}{dt} = \mu(p_i S^0 - S_i) - \lambda_i S_i, \\ \dfrac{dI}{dt} = \sum\limits_{k=1}^{n} \lambda_k S_k - (\mu + \gamma + \delta) I, \\ \dfrac{dR}{dt} = \gamma I - (\mu + \xi) R. \end{cases} \tag{2.1}$$

The rate of infection for each infective group is given by

$$\lambda_i = \beta c \frac{I}{N} \alpha_i \quad i = 1, \ldots, n, \tag{2.2}$$

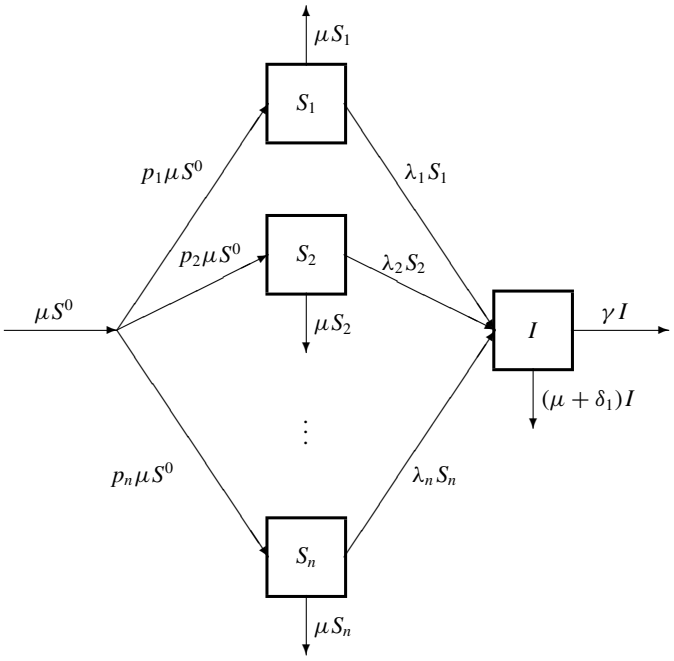

Fig. 2.1. Susceptible individuals enter the ith group, S_i, with a fraction p_i. The infectivity is the same for the whole infected population.

where α_i is the susceptibility of susceptible individuals in group i and $N = \sum_{i=1}^{n} S_i + I + R$.

In general, the number of contacts per person is a function of the population size such as $c = c(N)$. The choice of the function $c(N)$ then depends on the modeled disease or situations that we investigate. For certain diseases, such as influenza and measles, or in certain ranges of population sizes, the number of contacts are proportional to the population size, and for some other diseases, such as sexually-transmitted diseases, or at different situations where contacts are saturated, the number of contacts are constant. We consider all the cases in following sections.

3. No disease-induced mortality

Certain diseases, such as chickenpox and measles, are less fatal and the disease-induced mortality rate is much smaller than the other vital rates. Then, for simplification of the model formulation, we neglect the disease-induced deaths such that $\delta = 0$ and $\xi = 0$. We assume a general function $c(N)$ for the number of contacts.

The dynamics of the total population satisfy

$$\frac{dN}{dt} = \mu(S^0 - N).$$

Since $\lim_{t\to\infty} N(t) = S^0$, the dynamics of system (2.1) are qualitatively equivalent to the dynamics of its limiting system given by

$$\frac{dS_i}{dt} = \mu(p_i S^0 - S_i) - \eta\beta\alpha_i I S_i, \tag{3.1a}$$

$$\frac{dI}{dt} = \eta\beta I \sum_{k=1}^{n} \alpha_k S_k - (\mu + \gamma) I, \tag{3.1b}$$

where we have omitted the equation for R because the dynamics of the system are not affected by the dynamics of R, and we write $c(S^0)/S^0 := \eta$. (For dynamical behavior of limiting systems, interested readers are referred to [16].) Note that system (3.1) is positively time-invariant in set $G := \{S_i \geq 0,\ I \geq 0\}$. We then focus on the dynamics of (3.1) in set G hereafter in this section.

3.1. Reproductive number and the global stability of the infection-free equilibrium

System (3.1) has an infection-free equilibrium in which the component of infectives is zero and other susceptible components are positive. Denote this infection-free equilibrium by $E_0 := (S_i = p_i S^0, i = 1, \ldots, n, I = 0)$. Analyzing the local stability of E_0 gives the epidemic threshold conditions under which the number of infected individuals 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, such that E_0 is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.

We derive a formula for the reproductive number R_0 by investigating the local stability of E_0.

The Jacobian of (3.1) at E_0 has the form

$$J_1 := \begin{pmatrix} -\mu & 0 & \cdots & 0 & -\eta\beta S^0\alpha_1 p_1 \\ 0 & -\mu & \cdots & 0 & -\eta\beta S^0\alpha_2 p_2 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & -\mu & -\eta\beta S^0\alpha_n p_n \\ 0 & 0 & \ldots & 0 & -(\mu+\gamma)+\eta\beta S^0\sum_{i=1}^{n}\alpha_i p_i \end{pmatrix}.$$

All eigenvalues of J_1 have negative real part if and only if $-(\mu+\gamma)+\eta\beta S^0 \sum_{i=1}^{n}\alpha_i p_i < 0$. Therefore, the reproductive number can be defined as

$$R_0 := \frac{\eta\beta S^0}{\mu+\gamma}\sum_{i=1}^{n}\alpha_i p_i = \frac{c(S^0)\beta}{\mu+\gamma}\sum_{i=1}^{n}\alpha_i p_i. \tag{3.2}$$

Note that the mean number of contacts is $c(S^0) := r$, the mean duration of infection for this model is $\tau := 1/(\mu+\gamma)$, and the mean infectivity for each group is $\bar{\beta}_i := \beta\alpha_i$. We define the reproductive number for each group as

$$R_{0i} := \frac{r\beta\alpha_i}{\mu+\gamma} = r\bar{\beta}_i\tau.$$

The reproductive number of infection for the entire population can be expressed as the weighted average of the reproductive numbers of the groups such that

$$R_0 = \sum_{i=1}^{n} p_i R_{0i}. \tag{3.3}$$

Some recent mathematical epidemiological studies have demonstrated that a subcritical bifurcation may appear at the infection-free equilibrium which implies that even $R_0 < 1$ the modeled disease may spread in the population depending on initial infections, or that Hopf bifurcation may lead to periodicity for some epidemic models. (See, e.g. [17]). We prove that a subcritical bifurcation does not exist for model (3.1) or (2.1) by showing that if $R_0 < 1$ the infection-free equilibrium E_0 is globally asymptotically stable.

It follows from (3.1a) that

$$\frac{dS_i}{dt} \le \mu(p_i S^0 - S_i),$$

in set G, which implies

$$S_i(t) \le p_i S^0 + S_i(0)e^{-\mu t},$$

for all $t \geq 0$ in set G. Then, it follows from (3.1b) that

$$\begin{aligned} I(t) &= I(0)\exp\left(\eta\beta\sum_{i=1}^{n}\alpha_i\int_0^t S_i(u)du - (\mu+\gamma)t\right) \\ &\leq I(0)\exp\left(\left(\eta\beta S^0\sum_{i=0}^{n}\alpha_i p_i - (\mu+\gamma)\right)t + \frac{\eta\beta}{\mu}\sum_{i=0}^{n}\alpha_i S_i(0)\right) \\ &= I(0)\exp\left((\mu+\gamma)\left(\frac{\eta\beta S^0}{\mu+\gamma}\sum_{i=0}^{n}\alpha_i p_i - 1\right)t + \frac{\eta\beta}{\mu}\sum_{i=0}^{n}\alpha_i S_i(0)\right) \\ &= I(0)\exp\left(\frac{\eta\beta}{\mu}\sum_{i=0}^{n}\alpha_i S_i(0)\right)\exp\big((\mu+\gamma)(R_0-1)t\big) \to 0, \end{aligned}$$

as $t \to \infty$, for $R_0 < 1$, in set G.

Define set Ω by

$$\Omega := \{S_i \geq 0,\ i = 1, \ldots, n, \quad I = 0\}.$$

Then Ω is attractive for system (3.1) in G; that is, all solutions of (3.1) started in G approach set Ω. Therefore, to prove the global asymptotic stability of E_0 in G, we only need to show that $(p_1 S^0, p_2 S^0, \ldots, p_n S^0)$ is globally asymptotically stable in set Ω.

The global asymptotic stability of E_0 in Ω immediately follows from the fact that system (3.1a) in Ω is reduced to

$$\frac{dS_i}{dt} = \mu(p_i S^0 - S_i), \quad i = 1, \ldots, n, \tag{3.4}$$

and solutions of (3.4) are

$$S_i(t) = p_i S^0 - \Big(p_i S^0 - S_i(0)\Big)e^{-\mu t},$$

which approach $p_i S^0$, as $t \to \infty$ for $i = 1, \ldots, n$. In summary, we have

Theorem 3.1. *Define the reproductive number of infection, R_0, for system* (2.1) *as in* (3.2). *Then the infection-free equilibrium E_0 is globally asymptotically stable if $R_0 < 1$, and is unstable if $R_0 > 1$.*

3.2. Endemic equilibrium and its stability

We have shown in Section 3.1 that if $R_0 < 1$, infection-free equilibrium E_0 is the only equilibrium for (2.1), or (3.1), and is globally asymptotically stable, and that if $R_0 > 1$, E_0 is unstable. In this section, we assume $R_0 > 1$ and explore the dynamic behavior of (3.1). We first establish the existence and uniqueness of an endemic equilibrium, whose all components are positive, and then study its stability.

3.2.1. Existence and uniqueness of the endemic equilibrium
An endemic equilibrium of (3.1) satisfies the equations

$$\mu(p_i S^0 - S_i) - \eta\beta\alpha_i I S_i = 0, \quad i = 1, \dots, n, \tag{3.5}$$

$$\eta\beta I \sum_{k=1}^{n} \alpha_i S_k - (\mu + \gamma) I = 0. \tag{3.6}$$

Solving (3.5) for S_i gives

$$S_i = S^0 \frac{\mu p_i}{\mu + \eta\beta\alpha_i I}. \tag{3.7}$$

Substituting (3.7) into (3.6) then yields

$$\sum_{i=1}^{n} \frac{\mu S^0 \alpha_i p_i}{\mu + \eta\beta\alpha_i I} - \frac{\mu + \gamma}{\eta\beta} = 0. \tag{3.8}$$

Hence, there exists an endemic equilibrium if and only if there exists a positive solution I to (3.8).

Define $F(I)$ to be the left-hand side of (3.8). The derivative of $F(I)$ is given by

$$F'(I) = -\sum_{i=1}^{n} \frac{\mu\eta\beta S^0 \alpha_i^2 p_i}{(\mu + \eta\beta\alpha_i I)^2} < 0.$$

Hence $F(I)$ is a decreasing function. Note that

$$\lim_{I\to\infty} F(I) = -\frac{\mu + \gamma}{\eta\beta} < 0.$$

Then there exists a unique positive solution of $F(I) = 0$ if and only if $F(0) > 0$. Nevertheless,

$$F(0) = S^0 \sum_{i=1}^{n} \alpha_i p_i - \frac{\mu + \gamma}{\eta\beta} = \frac{\mu + \gamma}{\eta\beta} (R_0 - 1).$$

Therefore, there exists a unique endemic equilibrium if and only if $R_0 > 1$.

3.2.2. Stability of the endemic equilibrium
Let $(S_1^*, S_2^*, \dots, S_n^*, I^*)$ be the unique endemic equilibrium and we make the following transformation

$$I = I^*(1 + y), \qquad S_i = S_i^*(1 + x_i), \quad i = 1, \dots, n,$$

where $-1 < x_i < \infty$, $i = 1, \dots, n$, $-1 < y < \infty$. By substituting this transformation into (3.1), x_i and y satisfy the system

$$\begin{aligned} \frac{dx_i}{dt} &= -\left(\mu + \eta\beta\alpha_i I^*\right) x_i - \eta\beta\alpha_i I^* y - \eta\beta\alpha_i I^* x_i y, \\ \frac{dy}{dt} &= \eta\beta \sum_{i=1}^{n} \alpha_i S_i^* x_i + \eta\beta \sum_{i=1}^{n} \alpha_i S_i^* x_i y, \end{aligned} \tag{3.9}$$

and the stability of the endemic equilibrium of system (3.1) is equivalent to the stability of the trivial solution of system (3.9).

Define function V as

$$V(x_1, x_2, \ldots, x_n, y) := \sum_{i=1}^{n} \frac{S_i^* x_i^2}{2I^*} + y - \ln(1+y).$$

Then V is positive definite for $x_i > -1$ and $y > -1$, and $V = 0$ if and only if $(x_1, \ldots, x_n, , y) = (0, \ldots, 0)$. Along trajectories of system (3.9), we have

$$\begin{aligned}\frac{dV}{dt} &= -\sum_{i=1}^{n} \frac{S_i^* x_i}{I^*} \left((\mu + \eta\beta\alpha_i I^*)x_i + \eta\beta\alpha_i I^* y + \eta\beta\alpha_i I^* x_i y\right) \\ &\quad + \frac{y}{1+y}\eta\beta \sum_{i=1}^{n} \alpha_i S_i^* x_i (1+y) \\ &= -\sum_{i=1}^{n} \frac{S_i^* \mu}{I^*} x_i^2 - \eta\beta \sum_{i=1}^{n} \alpha_i S_i^* x_i^2 (1+y) \le 0.\end{aligned}$$

Moreover, the maximum invariant subset of set

$$\left\{ (x_1, \ldots, x_n, y) \;\middle|\; \frac{dV}{dt} = 0 \right\},$$

for $x_i > -1$ and $y > -1$, consists of only the origin $(0, \ldots, 0)$. Then, by Liapunov stability theory, the origin of system (3.9), and hence the endemic equilibrium of (3.1), is globally asymptotically stable. The results can be summarized below:

Theorem 3.2. *Suppose $R_0 > 1$ for system* (3.1). *Then there exists a unique positive endemic equilibrium of system* (3.1) *and it is globally asymptotically stable.*

4. Disease-induced mortality

Disease-induced mortality is crucial and cannot be ignored for many diseases. In this section, we let the disease-induced mortality rates δ and ξ be positive, and then consider when the number of contacts is either proportional or independent of the population size.

4.1. Contact number proportional to the population size

The contact patterns of transmission for certain diseases are random and for small populations the number of contacts can be assumed proportional to the total population size, that is, $c(N) := c_0 N$. Then the incidence of infection has a bilinear form. The model equations in this case are almost identical to (3.1) except γ in (3.1) is replaced by $\gamma + \delta$. Therefore, the results for this case are similar to the results for the case of no disease-induced mortality in Section 3. Write $\bar{\tau} = 1/(\mu + \gamma + \delta)$. The reproductive number for this case can be defined as $\sum_{i=1}^{n} p_i R_{0i}$ with

$$R_{0i} = \frac{c_0 S^0 \beta \alpha_i}{\mu + \gamma + \delta} = \bar{r}\bar{\beta}_i \bar{\tau},$$

where $\bar{r} = c_0 S^0$ is the total number of contacts, $\bar{\beta}_i = \beta\alpha_i$ is the mean probability of transmission, and $\bar{\tau}$ is the mean duration of infection. The infection-free equilibrium is globally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$. The endemic equilibrium exists if and only if $R_0 > 1$ and is always globally asymptotically stable if it exists.

4.2. Constant number of contacts

For many diseases, the contact rate is weakly dependent on the total population size or is saturated to a constant level. In this section, we assume that the number of contacts per individual, per unit of time is constant, i.e., $c(N) := r$, and that the incidence of infection has the standard form

$$\lambda_i = \frac{r\beta I}{N}\alpha_i, \tag{4.1}$$

where $N = \sum_{i=1}^{n} S_i + I$ [15]. Here we again assume that the individuals in group R do not contribute to the disease transmission and omit the equation for R in (2.1) to obtain

$$\begin{cases} \dfrac{dS_i}{dt} = \mu(p_i S^0 - S_i) - \lambda_i S_i, \\ \dfrac{dI}{dt} = \sum\limits_{k=1}^{n} \lambda_k S_k - (\mu + \gamma + \delta) I, \end{cases} \tag{4.2}$$

with λ given in (4.1).

4.2.1. Reproductive number and the global stability of the infection-free equilibrium

A formula for the reproductive number for system (4.2) can be derived in a similar way as that for system (3.1) by investigating the local stability of the infection-free equilibrium of (4.2), which is again written as E_0. The Jacobian at E_0 has the form

$$J_3 := \begin{pmatrix} -\mu & 0 & \cdots & 0 & -r\beta\alpha_1 p_1 \\ 0 & -\mu & \cdots & 0 & -r\beta\alpha_2 p_2 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & -\mu & -r\beta\alpha_n p_n \\ 0 & 0 & \ldots & 0 & -(\mu+\gamma+\delta) + r\beta \sum\limits_{i=1}^{n} \alpha_i p_i \end{pmatrix}.$$

Matrix J_3 has all eigenvalues with negative real part if and only if $-(\mu + \gamma + \delta) + r\beta \sum_{i=1}^{n} \alpha_i p_i < 0$. The reproductive number for each group in this case can be defined as

$$R_{0i} := \frac{r\beta}{\mu + \gamma + \delta}\alpha_i = r\bar{\beta}_i\bar{\tau},$$

and the reproductive number of infection for the entire population is again the following weighted average of these R_{0i}:

$$R_0 := \sum_{i=1}^{n} p_i R_{0i}. \tag{4.3}$$

The proof of the globally asymptotic stability of E_0 is similar to the proof in Section 3. We skip the details of the proof and summarize the results for model (4.2) in the following theorem.

Theorem 4.1. *Define the reproductive number of infection, R_0, for system* (4.2) *as in* (4.3)*. Then, the infection-free equilibrium of system* (4.2) *is globally asymptotically stable if $R_0 < 1$, and is unstable if $R_0 > 1$.*

4.2.2. Endemic equilibrium and its stability

Now we assume $R_0 > 1$. As before, we first show the existence and uniqueness of an endemic equilibrium.

An endemic equilibrium satisfies

$$\mu(p_i S^0 - S_i) - \lambda_i S_i = 0, \tag{4.4}$$

$$\sum_{k=1}^{n} \lambda_k S_k - (\mu + \gamma + \delta) I = 0. \tag{4.5}$$

To simplify notation we write $T = \sum_{i=1}^{n} S_i$ and let $\sigma = \gamma + \delta$. It follows from

$$\sum_{i=1}^{n} \mu(p_i S^0 - S_i) = \sum_{i=1}^{n} \lambda_i S_i = (\mu + \sigma) I$$

that $\mu(S^0 - T) = (\mu + \sigma) I$. Hence

$$T = S^0 - \left(1 + \frac{\sigma}{\mu}\right) I,$$

and

$$N = T + I = S^0 - \frac{\sigma}{\mu} I. \tag{4.6}$$

Substituting (4.6) into (4.4) and solving for S_i, we have

$$S_i = \frac{S^0(\mu S^0 - \sigma I) p_i}{r\beta\alpha_i I + (\mu S^0 - \sigma I)}. \tag{4.7}$$

Substituting (4.7) into (4.6), we obtain

$$(\mu S^0 - \sigma I) S^0 \sum_{i=1}^{n} \frac{p_i}{r\beta\alpha_i I + (\mu S^0 - \sigma I)} - S^0 + \left(1 + \frac{\sigma}{\mu}\right) I = 0. \tag{4.8}$$

Hence, there exists an endemic equilibrium if and only if there exists a positive solution, $0 < I < \mu S^0/\sigma$, to (4.8).

Define $F(I)$ to be the left-hand side of (4.8). Then $F(0) = 0$ and $F(\mu S^0/\sigma) = \frac{\mu}{\sigma} S^0 > 0$. Since

$$F'(I) = -\sigma S^0 \sum_{i=1}^{n} \frac{p_i}{r\beta\alpha_i I + (\mu S^0 - \sigma I)} - (\mu S^0 - \sigma I) S^0 \sum_{i=1}^{n} \frac{(r\beta\alpha_i - \sigma) p_i}{\left(r\beta\alpha_i I + (\mu S^0 - \sigma I)\right)^2} + 1 + \frac{\sigma}{\mu}, \quad (4.9)$$

we have

$$F'(0) = 1 - \frac{r\beta}{\mu} \sum_{i=1}^{n} \alpha_i p_i + \frac{\sigma}{\mu} = \frac{\mu + \sigma}{\mu}(1 - R_0). \quad (4.10)$$

Note that the second derivative of $F(I)$, given by

$$F''(I) = 2(\mu S^0 - \sigma I) S^0 \sum_{i=1}^{n} \frac{(r\beta\alpha_i - \sigma)^2 p_i}{\left(r\beta\alpha_i I + (\mu S^0 - \sigma I)\right)^3}, \quad (4.11)$$

is always positive for $I \leq \mu S^0/\sigma$. Hence the curve defined by $F(I)$ is concave upward on the interval $0 < I \leq \mu S^0/\sigma$. Therefore, if $R_0 \leq 1$, which implies $F'(0) \geq 0$, the curve of $F(I)$ does not cross the positive I axis; that is, there is no positive endemic equilibrium. On the other hand, if $R_0 > 1$, then $F'(0) < 0$. The curve of $F(I)$ has a unique intersection with the I axis on the interval $0 < I \leq \mu S^0/\sigma$. Substituting this positive solution of $F(I) = 0$ into (4.7), we obtain the component for S_i and hence a unique positive endemic equilibrium. Hence there exists a unique positive endemic equilibrium if only if $R_0 > 1$.

Next, we establish the stability of the endemic equilibrium. Write

$$a_i := S_i \frac{\lambda_i}{N}, \qquad b_i := S_i \frac{r\beta\alpha_i}{N} = (\mu + \sigma) \frac{S_i R_{0i}}{N},$$

where S_i are N are evaluated at the positive endemic equilibrium. Notice that $\sum_{i=1}^{n} b_n = \sum_{i=1}^{n} r\beta\alpha_i S_i/N = \sum_{i=1}^{n} \lambda_i S_i/I = \mu + \sigma$ at the endemic equilibrium. The Jacobian matrix at the endemic equilibrium can be expressed as

$$J_4 := \begin{pmatrix} -\mu - \lambda_1 + a_1 & a_1 & \cdots & a_1 & a_1 - b_1 \\ a_2 & -\mu - \lambda_2 + a_2 & \cdots & a_2 & a_2 - b_2 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_n & a_n & \cdots & -\mu - \lambda_n + a_n & a_n - b_n \\ \lambda_1 - \sum_{i=1}^{n} a_i & \lambda_2 - \sum_{i=1}^{n} a_i & \cdots & \lambda_n - \sum_{i=1}^{n} a_i & -\sum_{i=1}^{n} a_i \end{pmatrix}.$$

By using the $(n+2)\times(n+2)$ similarity matrix

$$M := \begin{pmatrix} 1 & -1 & -1 & \cdots & -1 & -1 \\ 0 & 1 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 1 & 0 \\ 0 & 0 & 0 & \cdots & 0 & 1 \end{pmatrix},$$

J_4 is transformed into $M^{-1}J_4M := H$, where

$$H = \begin{pmatrix} -\mu & 0 & 0 & \cdots & 0 & -\sigma \\ a_2 & -\mu-\lambda_2 & 0 & \cdots & 0 & -b_2 \\ a_3 & 0 & -\mu-\lambda_3 & \cdots & 0 & -b_3 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ a_n & 0 & 0 & \cdots & -\mu-\lambda_n & -b_n \\ \lambda_1 - \sum_{i=1}^{n} a_i & \lambda_2-\lambda_1 & \lambda_3-\lambda_1 & \cdots & \lambda_n-\lambda_1 & -\lambda_1 \end{pmatrix}. \tag{4.12}$$

Hence the endemic equilibrium is locally asymptotically stable if all eigenvalues of H have negative real part.

Let ρ be an eigenvalue of H and a corresponding eigenvector be $X := (x_1, x_2, \ldots, x_{n+1})^T$. Then they satisfy the system of equations

$$(\mu+\rho)x_1 = -\sigma x_{n+1}, \tag{4.13}$$

$$(\mu+\lambda_i+\rho)x_i = a_i x_1 - b_i x_{n+1}, \quad i = 2, \ldots, n, \tag{4.14}$$

$$(\lambda_1+\rho)x_{n+1} = -\sum_{i=1}^{n} a_i x_1 + \sum_{i=1}^{n} \lambda_i x_i - \lambda_1 \sum_{i=2}^{n} x_i. \tag{4.15}$$

It follows from (4.13) that

$$x_{n+1} = -\frac{\mu+\rho}{\sigma} x_1. \tag{4.16}$$

Substituting (4.16) into (4.14) yields

$$x_i = \frac{\sigma a_i + (\mu+\rho)b_i}{\sigma(\rho+\mu+\lambda_i)} x_1, \qquad i = 2, \ldots, n. \tag{4.17}$$

Then, substituting (4.16) and (4.17) into (4.15), we arrive at the characteristic equation

$$-\frac{(\lambda_1+\rho)(\mu+\rho)}{\sigma} + \sum_{i=1}^{n} a_i - \lambda_1 + \sum_{i=2}^{n} (\lambda_1-\lambda_i)\frac{\sigma a_i + (\mu+\rho)b_i}{\sigma(\mu+\lambda_i+\rho)} = 0. \tag{4.18}$$

Write $\rho = u + iv$. By substituting it into (4.18) and separating the real and imaginary parts, u and v satisfy the equations

$$-\frac{(\lambda_1+u)(\mu+u)-v^2}{\sigma}+\sum_{i=1}^{n}a_i-\lambda_1 + \sum_{i=2}^{n}(\lambda_1-\lambda_i)\frac{\big(\sigma a_i+(\mu+u)b_i\big)\big(\mu+\lambda_i+u\big)+b_iv^2}{\sigma\big((\mu+\lambda_i+u)^2+v^2\big)}=0, \quad (4.19)$$

$$-\frac{\lambda_1+\mu+2u}{\sigma}-\sum_{i=2}^{n}(\lambda_1-\lambda_i)\frac{\sigma a_i-\lambda_i b_i}{\sigma\big((\mu+\lambda_i+u)^2+v^2\big)}=0. \quad (4.20)$$

Since

$$\sigma a_i-\lambda_i b_i=\sigma\frac{S_i\lambda_i}{N}-\lambda_i(\mu+\sigma)\frac{S_iR_{0i}}{N}=\frac{\sigma S_i\lambda_i}{N}\left(1-\frac{R_{0i}(\mu+\sigma)}{\sigma}\right),$$

(4.20) is equivalent to

$$-\frac{\lambda_1+\mu+2u}{\sigma}-\sum_{i=2}^{n}\frac{S_i\lambda_i(\lambda_1-\lambda_i)}{N\big((\mu+\lambda_i+u)^2+v^2\big)}\left(1-\frac{R_{0i}(\mu+\sigma)}{\sigma}\right)=0. \quad (4.21)$$

System (4.2) is symmetric for the susceptible groups S_i. Without loss of generality, we assume that group S_1 is the least susceptible group such that $\alpha_1 \le \alpha_i$, $i = 2, \dots, n$. Then $\lambda_1 \le \lambda_i$, and $R_{01} \le R_{0i}$, $i = 2, \dots, n$. If we assume $R_{0i} \ge \sigma/(\mu+\sigma)$, for all $i \ge 2$, then the left-hand side of (4.21) is less than zero if $u \ge 0$; that is, there is a solution to (4.21) only if $u < 0$. Therefore matrix H has only eigenvalues with negative real part, which implies that the endemic equilibrium is locally asymptotically stable.

Results based on the most susceptible group can be also derived in a similar fashion. Without loss of generality, we assume that group S_1 is the most susceptible group such that $\alpha_1 \ge \alpha_i$, $i = 2, \dots, n$. Then $\lambda_1 \ge \lambda_i$, and $R_{01} \ge R_{0i}$, $i = 2, \dots, n$. If we assume now that $R_{0i} \le \sigma/(\mu+\sigma)$, for all $i \ge 2$, the left-hand side of (4.21) is less than zero if $u \ge 0$, which implies that there is no eigenvalue of H with nonnegative real part, or the local stability of the endemic equilibrium.

In summary, we have

Theorem 4.2. *Suppose $R_0 > 1$ such that the endemic equilibrium exists. Then the endemic equilibrium is locally asymptotically stable if either the reproductive number of each group, except the least susceptible group, is greater than or equal to $(\gamma+\delta)/(\mu+\gamma+\delta)$, that is*

$$R_{0i}=\frac{r\beta\alpha_i}{\mu+\gamma+\delta}\ge\frac{\gamma+\delta}{\mu+\gamma+\delta}, \qquad i=1,\dots,n, \quad i\ne j, \quad \text{(H1a)}$$

where S_j is the least susceptible group, or the reproductive number of each group, except the most susceptible group, is less than or equal to $(\gamma+\delta)/(\mu+\gamma+\delta)$, that is

$$R_{0i}=\frac{r\beta\alpha_i}{\mu+\gamma+\delta}\le\frac{\gamma+\delta}{\mu+\gamma+\delta}, \qquad i=1,\dots,n, \quad i\ne k, \quad \text{(H1b)}$$

where S_k is the most susceptible group.

If the reproductive number for each group is greater than one, then condition (H1a) in Theorem 4.2 is satisfied. Hence we have

Corollary 4.3. *Assume that the reproductive number of each group is greater than one, that is*

$$R_{0i} = \frac{r\beta\alpha_i}{\mu+\gamma+\delta} > 1, \qquad i = 1, \ldots, n.$$

Then the endemic equilibrium is locally asymptotically stable.

On the other hand, it is not necessary to have all reproductive numbers greater than one to satisfy the assumptions in Theorem 4.2. Some of them can be less than one, but because of $R_0 > 1$, some of them must be greater than one. Moreover, again because of $R_0 > 1$, if $R_{0i} \le (\gamma+\delta)/(\mu+\gamma+\delta)$, except the most susceptible group S_k, due to

$$1 < R_0 \le p_k R_{0k} + \frac{\gamma+\delta}{\mu+\gamma+\delta}(1-p_k),$$

the most susceptible group S_k must have

$$R_{0k} > \frac{\gamma+\delta}{\mu+\gamma+\delta} + \frac{\mu}{p_k(\mu+\gamma+\delta)}. \tag{4.22}$$

5. Summary and discussion

We have formulated compartmental differential susceptibility models in various settings. The susceptible population is subdivided into n subgroups based on their susceptibilities. We then considered the cases where the disease-induced mortality is either negligible or non-negligible, and the cases where the number of contacts is either proportional to the total population size or a constant.

For the cases where either the disease-induced mortality is negligible or the number of contacts is proportional to the total population, we have bilinear incidence of infection for either the limiting system, or the original system. We derived an explicit formula for the reproductive number, R_0, and showed that the infection-free equilibrium, whose component of infectives is zero, is globally asymptotically stable if $R_0 < 1$, and is unstable if $R_0 > 1$. As $R_0 > 1$, we further proved that there exists a unique endemic equilibrium with all components positive and it is always locally asymptotically stable whenever it exists.

When the disease-induced mortality is not negligible or the number of contacts is constant, we derived an explicit formula for the reproductive number, R_0, and showed that the infection-free equilibrium is globally asymptotically stable if $R_0 < 1$, and is unstable if $R_0 > 1$. When $R_0 > 1$, we proved the existence and uniqueness of the endemic equilibrium, but we have only obtained certain sufficient conditions of its stability.

The explicit formulas of R_0 for the models in this paper well fit in the calculations of R_0 for a variety of epidemiological models in the literature [18–21]. 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 whole population, R_0, is defined as a weighted average of those R_{0i}, weighted by the distribution of the influx into the susceptible subgroups.

Sensitivity studies of the disease prevention then can be based on the formula of such a weighted average of R_{0i}. For example, in order to set an efficient strategy in controlling disease transmission, we can identify more susceptible groups and make efforts to reduce the influx into those groups. Our study for the DS models can also help establish other effective strategies.

Suppose we have two different vaccination strategies one of which vaccinates the whole population with the susceptibility reduced to 50% for every individual, and one of which vaccinates only a half of the population with full efficacy such that the vaccinated individuals are fully immune to the disease. We assume there is disease-induced death and the contact number is constant such that the two models are based on system (4.2). Then the transmission dynamics for the former case are governed by

$$\begin{aligned} \frac{dS}{dt} &= \mu(S^0 - S) - \frac{r\beta\alpha I}{2(S+I)}S, \\ \frac{dI}{dt} &= \frac{r\beta\alpha S}{2(S+I)}I - (\mu+\gamma+\delta)I, \end{aligned} \tag{5.1}$$

and transmission dynamics for the latter case are described by

$$\begin{aligned} \frac{dS_1}{dt} &= \mu\left(\frac{1}{2}S^0 - S_1\right), \\ \frac{dS_2}{dt} &= \mu\left(\frac{1}{2}S^0 - S_2\right) - \frac{r\beta\alpha I}{S_1+S_2+I}S_2, \\ \frac{dI}{dt} &= \frac{r\beta\alpha S_2}{S_1+S_2+I}I - (\mu+\gamma+\delta)I. \end{aligned} \tag{5.2}$$

Using the same technique as before, we can show that the reproductive numbers for systems (5.1) and (5.2) are the same as

$$R_0^{\text{new}} = \frac{1}{2}R_0^{\text{old}} = \frac{1}{2}r\bar{\beta}\tau,$$

where R_0^{old} is the reproductive number when no vaccine is given. Hence there is no difference as the initial infection starts. However, simple calculations show that the infectives at the endemic equilibrium for system (5.1), denoted by $I^{(1)}$, and for system (5.2), denoted by $I^{(2)}$, are

$$I^{(1)} = \frac{\left(R_0^{\text{new}} - 1\right)\mu S^0}{(\mu+\gamma+\delta)\left(R_0^{\text{new}} - 1\right) + \mu}, \quad I^{(2)} = \frac{\left(R_0^{\text{new}} - 1\right)\mu S^0}{(\mu+\gamma+\delta)\left(2R_0^{\text{new}} - 1\right) + \mu}.$$

Therefore, while there is no difference for the early stage of infection between the two strategies if the disease can be completely eradicated, for diseases that are ineradicable, the second strategy can reduce the infection to a significantly lower level, comparing to the first strategy, if the reproductive number is very large.

We shall also point out that the DS models introduced in this paper can be applied to predator-prey or host-parasitoid interactions as well. We demonstrate it by applying it to predator-prey interactions.

To describe simple predator-prey dynamics, the following system is often used:

$$\frac{dN}{dt} = f(N) - g(N, P)P,$$
$$\frac{dP}{dt} = hg(N, P)P - dP,$$

where N and P are the prey and predator populations, $f(N)$ is the growth function of the prey, $g(N, P)$ is the predator per-capita consumption rate of prey or the functional response, h is the trophic efficiency, and d is the per-capita predator death rate. The classical Lotka-Volterra models adopt the principle of mass action such that the response of the predation is proportional to the product of their biomass densities. Then $g(N, P)P = bNP$ where b is a positive constant [22,23]. Newly developed ratio-dependent predator-prey theory, on the other hand, assumes ratio-dependent per-capita functional response such that

$$g(N, P)P = \frac{mNP}{wP + N},$$

where m is the maximum predator attack rate, and w is the prey density while the attack rate is half-saturated [23–26].

In our DS models, the n susceptible subgroups can be used for n prey populations, and the infective group can be used for a predator population. Then, the n prey populations are linked by their common predator. For the cases of no disease-induced mortality or the number of contacts proportional to the total population, the bilinear incidence of infection corresponds to the predation interaction of mass action, and if disease-induced mortality is included or a constant number of contacts is assumed, the standard incidence of infection corresponds to the ratio-dependent predation interaction where the prey density is one at a half-saturated attack rate. Different from the classical predator-prey models where the prey population follows the logistic growth in the absence of predation, the prey populations are assumed constant asymptotically in the case of no predator in our models. Based on these assumptions, the results that we obtained for the DS models indicate that there exist thresholds determining either the multiple prey populations survive while the predator goes to extinct, or all species co-exist. Although our DS models only describe the special case of the predation with $h = 1$ and $w = 1$, the analysis in this paper can be also employed to the more general case where $h \neq 1$ and $w \neq 1$.

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