An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations

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Received 1 February 1999; received in revised form 14 May 1999; accepted 18 May 1999

Abstract

The thresholds for mathematical epidemiology models specify the critical conditions for an epidemic to grow or die out. The reproductive number can provide significant insight into the transmission dynamics of a disease and can guide strategies to control its spread. We define the mean number of contacts, the mean duration of infection, and the mean transmission probability appropriately for certain epidemiological models, and construct a simplified formulation of the reproductive number as the product of these quantities. When the spread of the epidemic depends strongly upon the heterogeneity of the populations, the epidemiological models must account for this heterogeneity, and the expressions for the reproductive number become correspondingly more complex. We formulate several models with different heterogeneous structures and demonstrate how to define the mean quantities for an explicit expression for the reproductive number. In complex heterogeneous models, it seems necessary to define the reproductive number for each structured subgroup or cohort and then use the average of these reproductive numbers weighted by their heterogeneity to estimate the reproductive number for the total population. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Epidemiology; Mathematical model; Threshold conductors; Reproductive number; Transmission dynamics; Endemic equilibrium; Dynamical systems; Stability

1. Introduction

One of the fundamental questions of mathematical epidemiology is to find threshold conditions that determine whether an infectious disease will spread in a susceptible population when the

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PII: S0025-5564(00)00025-0
disease is introduced into the population. The threshold conditions are characterized by the so-called reproductive number, the reproduction number, the reproductive ratio, basic reproductive value, basic reproductive rate, or contact number, commonly denoted by \( R_0 \) in mathematical epidemiology \([5,10,17,19–21,23,29,35,39,43]\). The concept of \( R_0 \), introduced by Ross in 1909 \([39]\), is defined in epidemiological modeling such that if \( R_0 < 1 \), the modeled disease dies out, and if \( R_0 > 1 \), the disease spreads in the population.

There have been intensive studies in the literature to calculate \( R_0 \) for a wide class of epidemiological models of infectious diseases \([6,8,9,12,17,18,25,26,28,30,32–34,41]\). In mathematical models, the reproductive number is determined by the spectral radius of the next-generation operator in continuous models and, in particular, is determined by the dominant eigenvalue of the Jacobian matrix at the infection-free equilibrium for models in a finite-dimensional space \([8,9,24,27]\). It can also be obtained, in certain models, by suitable Lyapunov functions \([28,41]\).

The biological meaning of the reproductive number is the average number of secondary cases produced by one infected individual during the infected individual’s entire infectious period when the disease is first introduced. Let \( r \) be the average number of contacts per unit of time per individual, \( b \) be the probability of transmitting the infection per contact, and \( s \) be the mean duration of the infectious period. Then the reproductive number can be estimated by the following intuitive formula:

\[
R_0 = rf \beta \tau.
\]

This formula can give insight into the transmission dynamics of infectious diseases for various relatively simple epidemiological models \([3–5,7,40]\).

For simple homogeneous models, it is easy to define \( r, \beta, \) and \( \tau \). For example, consider a simple homogeneous AIDS model governed by the following system of ordinary differential equations:

\[
\begin{align*}
\frac{dS}{dt} &= \mu (S^0 - S(t)) - \lambda (t) S(t), \\
\frac{dI}{dt} &= \lambda (t) S(t) - (\mu + \nu) I(t), \\
\frac{dA}{dt} &= \nu I(t) - \delta A(t),
\end{align*}
\]

where \( S, I, \) and \( A \) denote the individuals susceptible to infection, the infected individuals, and the AIDS cases, respectively; \( \mu S^0 \) is the input flow into the susceptible group; \( \mu \) the removal rate; \( \nu \) the rate of contracting AIDS; \( \delta \) the removal rate due to the death from AIDS or other reasons; and \( \lambda \) the rate of infection given by

\[
\lambda (t) = \beta r \frac{I(t)}{S(t) + I(t)}.
\]

Here, \( \beta \) is the transmission probability per contact and \( r \) is the average number of contacts per individual per unit of time. We assume here that transmission by the AIDS cases is neglected. To focus our attention on the issues we will address, we assume, for simplicity, that the mixing is proportional for this model and other models in this paper.

The system has the infection-free equilibrium \((S^0, 0)\). The stability of \((S^0, 0)\) determines the reproductive number as
Formula (1.1) then holds when we define the duration of infection as \( \tau \text{ def } = 1/(\mu + v) \). (We will use the symbol \( \text{ def} \) to indicate that the equation is the definition of a quantity.)

However, as more heterogeneous structures or subgroups for the infected population are included in an epidemiological model, the calculation of \( R_0 \) becomes more complicated, and it is difficult to find an explicit formula for \( R_0 \). Even when an explicit formula can be obtained, it is not always clear whether it is appropriate to define a mean contact rate, a mean duration of infection, and a mean transmission probability so that the reproductive number can still be estimated by formula (1.1). Furthermore, even if it can be claimed that such an estimate is adequate, a deep understanding of the model is absolutely necessary so that those means can be well defined.

Moreover, for models of the diseases for which differentiation of the contact rates or the partner acquisition rates must be addressed, such as sexually transmitted disease (STD) models, not only the mean but also the second moment or the variance about the mean must be taken into account. Then, formula (1.1) can no longer be applied. For certain simple models, a more accurate formula for the reproductive number is

\[
R_0 = \frac{r\beta}{\mu + v}.
\]

where \( r \) is the mean number of contacts per individual and \( \sigma \) is the variance or standard deviation of the mean number of contacts [1–3,5,8,28,36].

Formula (1.2) is an effective formulation for providing insight into the transmission dynamics of diseases. Unfortunately, as more heterogeneities are considered, it becomes impracticable to define the variance or the standard deviation, and expression (1.2) becomes inadequate.

For risk-group models, Hethcote and Yorke [23] first introduced and Jacquez et al. [28,29] specified the idea of defining a mean reproductive number as the average number of infected individuals generated per infected individual over the duration of the infected state. They defined a reproductive number for each subgroup and then express the mean reproductive number as a weighted mean of those group reproductive numbers.

In this paper, we use the models in [26] as a basis and formulate new heterogeneous models to demonstrate how different cases can be treated so that an appropriate reproductive number can be estimated. We show that for models with no risk structure, that is, the models with a homogeneous susceptible population in the contact rates, it is still possible to define the mean quantities and to apply formula (1.1). We show, however, for susceptible populations with heterogeneous structure such as risk structure and age structure, it is more appropriate to define a reproductive number for each subgroup or each cohort and then express the reproductive number for the whole population as the weighted average of those reproductive numbers for the subgroups or cohorts.

2. Models without risk structure

We first consider the models in which the risk level is assumed to be uniform for all the susceptible individuals. The susceptible population may still be divided into subgroups, but they are not based on the risk level, that is, the number of partners, or the number of contacts.
2.1. Differential infectivity models

There is evidence that HIV serum and plasma levels or individual variations affect transmission, that infected individuals have different levels of virus after the acute phase, and that those with high levels progress to AIDS more rapidly than those with low levels in clinical studies. As a result, a hypothesis that some individuals are highly infectious over long periods of time and a new model that accounts only for differences between infected individuals, referred to as a differential infectivity (DI) HIV model, were proposed in [26]. In that DI model, it is assumed that individuals enter a specific group when they become infected and stay in that group until they are no longer involved in transmitting the disease. Their infectivity and progression rates to AIDS are assumed to depend upon which group they are in; the susceptible population is assumed to be homogeneous; and variations in susceptibility, risk behavior, and many other factors associated with the dynamics of the spread of HIV are neglected. In this section, we use the simple DI model formulated in [26] and generalize it to a model in which the risk level of infected individuals depends on the group to which they belong. We demonstrate how a mean number of contacts, a mean transmission probability, and a mean duration of infection can be defined so that formula (1.1) can be used to obtain the reproductive number.

The following DI model with homogeneous contact rate was formulated for HIV transmission in [26]

\[
\begin{align*}
\frac{dS}{dt} &= \mu(S^0 - S) - \lambda S, \\
\frac{dI_i}{dt} &= p_i \lambda S - (\mu + v_i)I_i, \quad i = 1, \ldots, n, \\
\frac{dA}{dt} &= \sum_{j=1}^n v_j I_j - \delta A,
\end{align*}
\]  

where the infected population is subdivided into \( n \) subgroups, \( I_1, I_2, \ldots, I_n \). Upon infection, an individual enters subgroup \( i \) with probability \( p_i \) and stays in this group until becoming inactive in transmission, where \( \sum_{i=1}^n p_i = 1 \). The variable \( A \) denotes the group of individuals removed from the population due to end stage disease or behavioral changes. Individuals in \( A \) are assumed to die at a rate \( \delta \geq \mu \). The rate \( v_j \) of leaving the infected population because of behavioral changes induced by either HIV-related illnesses or testing positive for HIV (presumably changing behavior so as not to transmit infection) depends on the subgroups.

The rate of infection \( \lambda \) depends on the transmission probability per contact of individuals in subgroup \( i \), \( \beta_i \), the proportion of individuals in the subgroup, \( I_i/N \), and the number of contacts of an individual per unit of time \( r \), so that

\[
\lambda(t) = r \sum_{i=1}^n \beta_i \frac{I_i(t)}{N(t)},
\]

where \( N(t) = S(t) + \sum_{j=1}^n I_j(t) \).
The reproductive number for this model is

\[ R_0 = r \sum_{i=1}^{n} \frac{p_i \beta_i}{\mu + v_i}. \]

By defining the mean duration of infectiousness for infected individuals and the mean probability of transmission as

\[ \bar{\tau} = \frac{1}{\mu + v_i}, \quad \bar{\beta} = \frac{1}{\bar{\tau}} \sum_{i=1}^{n} \frac{p_i \beta_i}{\mu + v_i}, \]

respectively, the reproductive number can be expressed as the product of the number of contacts and these two means

\[ R_0 = r \bar{\beta} \bar{\tau}. \]

Now we generalize the DI model (2.1) by assuming that the number of contacts per individual per unit of time depends on the subgroups, because people may change their behavior according to how ill they are. Let \( r_i \) be the average number of contacts per individual per unit of time in subgroup \( i \). Then the rate of infection is generalized to

\[ \lambda(t) = r \sum_{i=1}^{n} \beta_i \frac{r_i I_i(t)}{r S(t) + \sum_{j=1}^{n} r_j I_j(t)}, \]

where \( r \) is the contact rate of the susceptible individuals and \( r_i \) is the contact rate of infected individuals in subgroup. We refer to model (2.1) with the generalized infection rate as a general DI model.

Similarly as in [26], a simple stability analysis for the infection-free equilibrium gives the reproductive number for the general DI model as

\[ R_0 = \sum_{i=1}^{n} \frac{p r_i \beta_i}{\mu + v_i}. \]

The mean duration of infectiousness for infected individuals in this general DI model is the same as for model (2.1).

Since \( r_i/(\mu + v_i) \) is the average number of contacts per individual in group \( i \) made during the whole infection period, the total average number of contacts per infected individual during the whole infection period is

\[ r_{\text{total}} \overset{\text{def}}{=} \sum_{i=1}^{n} \frac{p r_i}{\mu + v_i}, \]

and hence the mean number of contacts per infected individual per unit time for the general DI model, denoted by \( \bar{r} \), is

\[ \bar{r} = \frac{r_{\text{total}}}{\bar{\tau}} = \frac{1}{\bar{\tau}} \sum_{i=1}^{n} \frac{p r_i}{\mu + v_i}. \]

The total transmission probability through all contacts with infected individuals in subgroup \( i \) during the entire time period when they are infected is
Hence, the mean probability per contact per unit of time for the general DI model, denoted by $\bar{\beta}$, is

$$\bar{\beta} \equiv \sum_{i=1}^{n} \frac{p_i \beta_i^{\text{total}}}{\bar{r} \tau} = \frac{1}{\bar{r} \tau} \sum_{i=1}^{n} \frac{p_i r_i \beta_i}{\mu + v_i}.$$ 

Therefore,

$$R_0 = \bar{r} \beta \tau.$$ 

### 2.2. The staged progression models

A common mathematical model for the spread of AIDS assumes that infected individuals pass through several stages, being highly infectious in the first few weeks after becoming infected, then having low infectivity for many years, and finally becoming gradually more infectious as their immune systems break down, and they progress to AIDS, with the rates of progression to AIDS being also very low in the first few years after infection. Based on this hypothesis, epidemiological models that we refer to as staged progression (SP) models have been studied by many researchers (see the references in [26]).

#### 2.2.1. The general discrete SP model

The following SP model with a homogeneous contact rate is studied in [26]. It assumes that the susceptible population is homogeneous and is maintained by the same type of inflow. It assumes that the population of infected individuals is subdivided into subgroups $I_1, I_2, \ldots, I_n$ with different infection stages such that infected susceptible individuals enter the first subgroup $I_1$ and then gradually progress from this subgroup to subgroup $I_n$. Let $\gamma_i$ be the average rate of progression from subgroup $i$ to subgroup $i+1$, for $i = 1, \ldots, n-1$, and let $\gamma_n$ be the rate at which infected individuals in subgroup $I_n$ become sexually inactive or no longer infectious due to end-stage disease or behavioral changes. The dynamics of the transmission are governed by the following system:

\[
\begin{align*}
\frac{dS}{dt} &= \mu(S^0 - S) - \lambda S, \\
\frac{dI_1}{dt} &= \lambda S - (\gamma_1 + \mu)I_1, \\
\frac{dI_i}{dt} &= \gamma_{i-1}I_{i-1} - (\gamma_i + \mu)I_i, \quad 2 \leq i \leq n, \\
\frac{dA}{dt} &= \gamma_n I_n - \delta A, 
\end{align*}
\] 

(2.2)

where the infection rate $\lambda$ is given by
\[ \dot{\lambda} = r \sum_{i=1}^{n} \beta_i \frac{I_i}{N}, \]  
\[ \text{(2.3)} \]

Here, \( r \) is the average number of contacts per individual per unit time, \( \beta_i \) the transmission probability per contact with an individual in subgroup \( i \), \( \delta \geq \mu \) the removal rate of individuals in group \( A \), and \( N = S + \sum_{i=1}^{n} I_i \). Notice again that the transmission by the \( A \) group is neglected just as it was in model (2.1).

The reproductive number for model (2.2) with (2.3) is defined by

\[ R_0 = r \sum_{i=1}^{n} \frac{\beta_i q_i}{\mu + \gamma_i}, \]

where

\[ q_i = \prod_{j=1}^{i-1} \frac{\gamma_j}{\mu + \gamma_j}. \]

The mean duration of infection is defined by

\[ \bar{\tau} = \sum_{i=1}^{n} \frac{q_i}{\mu + \gamma_i}, \]

and the mean probability of transmission per partner from an infected individual during the course of infection is defined by

\[ \bar{\beta} = \frac{1}{\bar{\tau}} \sum_{i=1}^{n} \frac{\beta_i q_i}{\gamma_i + \mu}. \]

Then, the reproductive number is again expressed as

\[ R_0 = r\bar{\beta}\bar{\tau}. \]

(See \[26\] for details.) Instead of assuming that all infected individuals have the same contact rate, we now assume that infected individuals with different stages may have different rates of contacts because of possible changes in behavior. Then the infection rate is given by

\[ \dot{\lambda} = r \sum_{i=1}^{n} \beta_i \frac{r_i I_i}{rS + \sum_{j=1}^{n} r_j I_j}. \]  
\[ \text{(2.4)} \]

Here, \( r \) is the average number of contacts per susceptible individual per unit of time, \( r_i \) the average number of contacts per infected individual with stage \( i \) per unit of time, \( \beta_i \) the transmission probability per contact with an infected individual in subgroup \( i \), and \( \delta \) is the removal rate of individuals in group \( A \).

The reproductive number for the general SP model given by (2.2) and (2.4) can be defined as

\[ R_0 = \sum_{i=1}^{n} \frac{r_i \beta_i q_i}{\mu + \gamma_i}. \]

The mean duration of infection for this model is the same as that for the SP model (2.2) with (2.3).
The term \( r_i q_i / (\mu + \gamma_i) \) is the number of contacts per infected individual during the individual’s infection period in subgroup \( i \). Then the total number of contacts that an infected individual makes during all of the individual’s infection period is

\[
\sum_{i=1}^{n} \frac{r_i q_i}{\mu + \gamma_i} \overset{\text{def}}{=} \rho_{\text{total}}.
\]

Hence, the average number of contacts per infected individual per unit of time is

\[
\bar{r} \overset{\text{def}}{=} \frac{\rho_{\text{total}}}{\bar{\tau}},
\]

so that \( \rho_{\text{total}} \overset{\text{def}}{=} \bar{r} \bar{\tau} \).

The transmission probability through all contacts with an infected individual in subgroup \( i \) is \( \beta_i r_i q_i / (\mu + \gamma_i) \). Then the total transmission probability from all contacts with an infected individual during the individual’s entire infection period, denoted by \( \beta_{\text{total}} \), can be defined as

\[
\beta_{\text{total}} \overset{\text{def}}{=} \sum_{i=1}^{n} \frac{\beta_i r_i q_i}{\mu + \gamma_i}.
\]

Hence, the average transmission probability per contact is

\[
\bar{\beta} \overset{\text{def}}{=} \frac{\beta_{\text{total}}}{\rho_{\text{total}}} = \frac{1}{\bar{r} \bar{\tau}} \sum_{i=1}^{n} \frac{\beta_i r_i q_i}{\mu + \gamma_i},
\]

and the reproductive number can be expressed as

\[
R_0 = \bar{r} \bar{\beta} \bar{\tau}.
\]

2.2.2. The continuous SP model

In this section, we consider a simple SIR (susceptible–infected–removed) STD model with continuous infection stages (see [25,42] for further references). Let \( u \) be the infection age, and denote the distribution functions of susceptible, infected, and removed individuals by \( S(t,u), I(t,u), \) and \( R(t) \), respectively. We again neglect the transmission by the group of removed individuals, assuming that they are a small portion of the infected population and that they are less active in transmitting the disease. We also neglect migration between populations and assume that the only recruitment into the population is a constant inflow of susceptible individuals and that all infected individuals are infectious and will eventually be removed.

Under these assumptions, the dynamics of the population are governed by the following system of equations and associated boundary conditions:

\[
\frac{dS}{dt} = \mu(S^0 - S) - \lambda(t)S,
\]

\[
\frac{\partial I}{\partial t} + \frac{\partial I}{\partial u} = -(\mu + \gamma(u))I,
\]

\[
I(t,0) = \lambda(t)S,
\]

\[
\]
\[ I(0, u) = \Psi(u), \]  
\[ \frac{dR}{dt} = -\delta R + \int_0^\infty \gamma(s)I(t, u)\,du, \]  
\[ \lambda(t) = r(0) \int_0^\infty \beta(u)r(u) \frac{I(t, u)}{r(0)S(t) + \int_0^\infty r(v)I(t, v)\,dv}\,du. \]

where \( \mu \) is the attrition rate caused by natural death or movement out of the sexually active population, \( \lambda \) the infection rate, \( \mu S_0 \) the rate at which individuals migrate into the population, \( \gamma \) the removal rate of infected individuals, \( \delta \) the death rate of individuals in the removed group, and \( \Psi \) is the initial distribution of the infected population.

We consider the infection rate that can be represented as

\[ \lambda(t) = r(0) \int_0^\infty \beta(u)r(u) \frac{I(t, u)}{r(0)S(t) + \int_0^\infty r(v)I(t, v)\,dv}\,du. \]

Here we assume that the individuals at different infection ages have different activity levels such that \( r(u) \) is the number of contacts that an infected individual with infection age \( u \) has, \( r(0) \) the number of contacts that a susceptible individual has, and \( \beta(u) \) is the probability that an infected partner with infection age \( u \) will infect a susceptible partner.

By linearizing \( S(t) \) and \( I(t, u) \) about \( (S_0, 0) \) and assuming the solutions initially change exponentially, a characteristic equation can be obtained. Analyzing the characteristic equation to locate the eigenvalues of the equation in the left-half complex plane yields the following formula for the reproductive number for the model governed by (2.5) and (2.6):

\[ R_0 = \int_0^\infty r(u)\beta(u) \exp \left\{ -\left( \mu u + \int_0^u \gamma(w)\,dw \right) \right\}\,du. \]

(Details of the derivation of formula (2.7) can be found in Appendix A.)

It is similar to the discrete SP models that the mean duration of infection is

\[ \bar{\tau} = \int_0^\infty \exp \left\{ -\left( \mu u + \int_0^u \gamma(w)\,dw \right) \right\}\,du, \]

the total contact rate is

\[ r^{\text{total}} = \int_0^\infty r(u) \exp \left\{ -\left( \mu u + \int_0^u \gamma(w)\,dw \right) \right\}\,du, \]

the mean number of contacts is

\[ \bar{r} = \frac{r^{\text{total}}}{\bar{\tau}} = \frac{1}{\bar{\tau}} \int_0^\infty r(u) \exp \left\{ -\left( \mu u + \int_0^u \gamma(w)\,dw \right) \right\}\,du, \]

the total transmission probability is

\[ \beta^{\text{total}} = \int_0^\infty r(u)\beta(u) \exp \left\{ -\left( \mu u + \int_0^u \gamma(w)\,dw \right) \right\}\,du, \]

and then the mean probability of transmission is

\[ \bar{\beta} = \frac{\beta^{\text{total}}}{\bar{r}^{\text{total}}} = \frac{1}{\bar{r}^{\text{total}}} \int_0^\infty r(u)\beta(u) \exp \left\{ -\left( \mu u + \int_0^u \gamma(w)\,dw \right) \right\}\,du. \]
Therefore, the reproductive number can be again expressed as
\[ R_0 = \bar{r}\bar{\beta}\bar{\tau}. \]

2.3. The differential susceptibility model

We have shown in Section 2.1 that for the DI model and the SP models, in so far as we assume a homogeneous susceptible population such that there is one group of susceptible individuals, the mean number of contacts, the mean transmission probability, and the mean duration of infection can be defined so that the reproductive number can be always given as the product of these three means. In this section, we consider a simple differential susceptibility (DS) model in which the infected population is homogeneous, but the susceptible population is divided into \( n \) groups according to their susceptibilities. The model equations are given by

\[
\begin{align*}
\frac{dS_i}{dt} &= \mu(S_i^0 - S_i) - \lambda_i S_i, \\
\frac{dI}{dt} &= \sum_{k=1}^{n} \lambda_k S_k - (\mu + \gamma)I, \\
\frac{dA}{dt} &= \gamma I - \delta A.
\end{align*}
\]  

(2.8)

The rate of infection is

\[
\lambda_i = \frac{r\beta I}{N} \chi_i, \quad i = 1, \ldots, n,
\]

(2.9)

where \( \chi_i \) is the susceptibility of susceptible individuals in subgroup \( i \), \( \beta \) the infectious rate of infected individuals, \( r \) the average number of contacts per sexually active individual, and \( N = \sum_{i=1}^{n} S_i + I \).

By the local stability analysis of the infection-free equilibrium, the reproductive number for model (2.8) with (2.9) can be defined as

\[
R_0 = \frac{r\beta \sum_{i=1}^{n} \chi_i S_i^0}{(\mu + \gamma) \sum_{i=1}^{n} S_i^0}.
\]

Since there is only one group of infected individuals, the mean duration is \( \tau \equiv 1/(\mu + \gamma) \). The biological definition of the reproductive number is the number of secondary cases produced when a primary case is introduced into a totally susceptible population. Hence, the mean susceptibility of susceptible individuals in all the groups, denoted by \( \bar{\chi} \), should be weighted by all susceptible groups at the infection-free equilibrium. That is,

\[
\bar{\chi} = \frac{\sum_{i=1}^{n} \chi_i S_i^0}{\sum_{i=1}^{n} S_i^0},
\]

and hence the total mean infectivity is \( \bar{\beta} \equiv \beta \bar{\chi} \). With these notations, the reproductive number can be rewritten as

\[ R_0 = r\bar{\beta}\bar{\tau}. \]
2.4. The combined DS and DI models

We showed in Section 2.3 that even if the susceptible population is divided into subgroups, whereas there is a homogeneous infected population, we can still define the mean infectivity, and the reproductive number can be given by the compact and intuitive formula. Now if the infected population is divided into subgroups based on their different infectivities and the average numbers of contacts of infected individuals in the infected subgroups are distinct, can those means be well defined and the reproductive number still be the product of those means? We combine the DS and DI models and derive the formula of the reproductive number as follows.

Divide the susceptible population into \( n \) groups according to their susceptibilities and the infected population into \( m \) groups based on their infectivities and how ill they are. Then we have the following system of equations:

\[
\begin{align*}
\frac{dS_i}{dt} &= \mu(S_i^0 - S_i) - \lambda_i S_i, \quad i = 1, \ldots, n, \\
\frac{dI_j}{dt} &= \sum_{k=1}^{m} p_{kj} \lambda_k S_k - (\mu + v_j)I_j, \quad j = 1, \ldots, m, \\
\frac{dA}{dt} &= \sum_{k=1}^{m} v_k I_k - \delta A,
\end{align*}
\]

(2.10)

where the fractions satisfy \( \sum_{j=1}^{m} p_{kj} = 1, \quad k = 1, \ldots, n. \)

The rate of infection is

\[
\lambda_i = rz_i \sum_{j=1}^{m} \beta_j \frac{r_j I_j}{\sum_{l=1}^{n} S_l + \sum_{k=1}^{m} r_k I_k},
\]

(2.11)

where \( r \) is the mean number of contacts per susceptible individual, \( r_j \) the average number of contacts per infected individual in subgroup \( j \), \( z_i \) the susceptibility of the susceptible individuals in subgroup \( i \), and \( \beta_j \) is the infectiousness of the infected individuals in subgroup \( j \).

By investigating the stability of the infection-free equilibrium, the reproductive number for the model given by (2.10) and (2.11) can be defined by

\[
R_0 = \sum_{j=1}^{m} \sum_{k=1}^{n} \frac{p_{kj} z_k S_k^0 r_j \beta_j}{(\mu + v_j) \sum_{j=1}^{n} S_j^0}.
\]

(2.12)

(The detailed proof of formula (2.12) is given in Appendix B.)

The infected individuals in each subgroup are infected from all susceptible subgroups. Their mean duration of infection needs to be weighed by the fractions and the sizes of susceptibles at the infection-free equilibrium. Denote the mean duration of infection by \( \bar{\tau} \). Then

\[
\bar{\tau} \overset{\text{def}}{=} \sum_{j=1}^{n} \frac{1}{(\mu + v_j)} \frac{\sum_{k=1}^{m} p_{kj} S_k^0}{\sum_{j=1}^{n} S_j^0}.
\]

The term \( r_j/(\mu + v_j) \) is the number of contacts per infected individual in group \( j \) during the whole duration of infection. Then,
\[ \sum_{k=1}^{n} \frac{r_j}{(\mu + v_j)} \frac{p_k S_0^j}{\sum_{i=1}^{n} S_i^0} \]

is the average number of contacts per infected individual in subgroup \( j \) during the whole infection period with susceptible individuals that induce the transmission of infection. Summing them over and dividing by the mean duration of infection gives the mean number of contacts per infected individual over all infected subgroups per unit of time \( \bar{r} \). That is,

\[ \bar{r} \overset{\text{def}}{=} \frac{1}{\bar{T}} \sum_{j=1}^{m} \sum_{k=1}^{n} \frac{r_j}{(\mu + v_j)} \frac{p_k S_0^j}{\sum_{i=1}^{n} S_i^0}. \]

The term \( r_j \beta_j / (\mu + v_j) \) is the total infectivity per infected individual in subgroup \( j \) through all contacts during the whole infection period. Since transmission of a disease results from the infectivity of infected individuals and the susceptibility of susceptible individuals, the probability of transmission per contact from an infected individual in subgroup \( j \) with all susceptible individuals during the whole infection period is

\[ \frac{r_j \beta_j}{\mu + v_j} \sum_{k=1}^{n} \frac{p_k S_0^j}{\sum_{i=1}^{n} S_i^0}. \]

Again, summing over all subgroups of infected individuals and dividing by the mean number of contacts and the mean duration of infection yields the mean probability of transmission

\[ \bar{\beta} \overset{\text{def}}{=} \frac{1}{\bar{r} \bar{T}} \sum_{j=1}^{m} \frac{r_j \beta_j}{\mu + v_j} \sum_{k=1}^{n} \frac{p_k S_0^j}{\sum_{i=1}^{n} S_i^0} = \frac{1}{\bar{r} \bar{T}} R_0. \]

Therefore, the reproductive number can be rewritten as \( R_0 = \bar{r} \bar{\beta} \).

3. The segregated risk DI model

In this section, we consider a segregated risk DI model. We divide the susceptible population into \( n \) groups based on their risk behavior. Then, each risk-based infected population group is further subdivided into \( m \) subgroups. Upon infection, a susceptible individual in the risk-group \( S_i \) enters infected subgroup \( I_j \) with probability \( p_j \) and stay in this subgroup until becoming inactive in transmission, where \( \sum_{j=1}^{m} p_j = 1 \). The rate at which infected individuals are removed from subgroup \( I_j \) to the group of removed individuals, \( R \), is \( v_j \). Again, we assume that individuals in group \( R \) are no longer actively transmitting disease. The model is then defined by the following system:

\[
\begin{align*}
\frac{dS_i}{dt} &= \mu(S_0^i - S_i) - \lambda_i S_i, & i = 1, \ldots, n, \\
\frac{dI_j}{dt} &= p_j \lambda_i S_i - (\mu + v_j) I_j, & j = 1, \ldots, m, \\
\frac{dR}{dt} &= \sum_{i=1}^{n} \sum_{j=1}^{m} v_j I_j - \delta R,
\end{align*}
\] (3.1)
where $\mu$ is the removal rate, including the natural death rate and other rates at which people leave the investigated population, $\mu S^0_i$ the recruitment of new susceptible individuals into the population with risk $i$, and $\delta$ is the death rate of individuals in group $R$.

The rate of infection for the individuals with risk $i$, $\lambda_i$, for proportional mixing, is defined by

$$\dot{\lambda}_i = \frac{\sum_{j=1}^{m} \beta_j \sum_{i=1}^{n} r_i I_j^i}{\sum_{k=1}^{n} r_k (S_k + \sum_{i=1}^{m} I_j^k)},$$

where $\beta_j$ is the infectivity of the individuals in the infected subgroup $I_j^i$ and is assumed to be independent of their risk level.

The reproductive number for model (3.1) with (3.2) can be defined by

$$R_0 = \sum_{i=1}^{n} \frac{\sum_{j=1}^{m} \sum_{j=1}^{n} p_j \beta_j}{\mu + \nu_j} \frac{r_i^2 S^0_i}{\sum_{i=1}^{n} r_i S^0_i}.$$ 

(We give a complete derivation of formula (3.3) in Appendix C.)

Note that if the removal rates $\nu_j = \nu_j$ are independent of risk level, then the reproductive number becomes

$$R_0 = \sum_{j=1}^{m} \frac{p_j \beta_j}{\mu + \nu_j} \sum_{i=1}^{n} \frac{r_i^2 S^0_i}{\sum_{i=1}^{n} r_i S^0_i}.$$ 

(3.4)

The term $\sum_{j=1}^{m} p_j \beta_j / (\mu + \nu_j)$ is the product of the mean duration of infection and the mean transmission probability. This $R_0$ in (3.4) involves the second mean of the risk level $\sum_{i=1}^{n} r_i^2 S^0_i$. As Diekmann et al. pointed out in [8],

$$\frac{\sum_{i=1}^{n} r_i^2 S^0_i}{\sum_{i=1}^{n} r_i S^0_i} = \frac{\text{mean} + \text{variance}}{\text{mean}}.$$ 

Hence, (3.4) is consistent with the results in [8,11,37].

However, if the removal rates are not risk-level independent, it is unclear how to define the mean duration of infection and the mean transmission probability. Here we provide an alternative way to make the formula of the reproductive number more intuitive.

Define the mean duration of infectivity for infected individuals with risk level $i$ by

$$\bar{\tau}_i \overset{\text{def}}{=} \sum_{j=1}^{m} \frac{p_j \beta_j}{\mu + \nu_j},$$

the mean probability of transmission per partner from those infected individuals by

$$\bar{\beta}_i \overset{\text{def}}{=} \frac{1}{\bar{\tau}_i} \sum_{j=1}^{m} \frac{p_j \beta_j}{\mu + \nu_j},$$

and the reproductive number for the subgroup with risk level $i$ by

$$R_0^i \overset{\text{def}}{=} r_i \bar{\beta}_i \bar{\tau}_i.$$ 

Then the reproductive number can be rewritten as
Here, \( r_i S_i^0 \) is the total number of contacts of an individual in the group with risk level \( i \). Then the reproductive number for the whole population is equal to the mean reproductive numbers of the risk groups weighted by their risks.

4. A simple age-structured model

We consider a simple SIR model with age structure in this section (see [33]). Denote the distribution functions of susceptible, infected, and removed individuals by \( S(t,a) \), \( I(t,a) \), and \( R(t,a) \), respectively, where \( t \) is the time and \( a \) is the age. We neglect transmission of the virus by group \( R \). We also neglect migration between populations and assume that the only recruitment into the population is a constant inflow of susceptible individuals.

Under these assumptions, the dynamics of the population are governed by the following system of equations and associated boundary conditions:

\[
\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = L(a) - (\mu(a) + \lambda(t,a))S, \\
S(t,a_0) = B, \\
S(0,a) = \Phi(a), \\
\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = - (\mu(a) + \gamma(a))I + \lambda(t,a)S, \\
I(t,a_0) = 0, \\
I(0,a) = \Psi(a), \\
\frac{\partial R}{\partial t} + \frac{\partial R}{\partial a} = - \delta(a)R + \gamma(a)I, \\
R(t,a_0) = 0, \\
R(0,a) = 0,
\]

where \( \mu \) is the attrition rate due to natural death or movement out of the sexually active population, \( \lambda \) the infection rate, \( B \) the number of individuals in the susceptible class at age \( a_0 \), \( L \) the rate at which individuals flow into the population at ages greater than \( a_0 \), \( \gamma \) the removal rate, \( \delta \) is the death rate in group \( R \), and \( \Phi \) and \( \Psi \) are the initial distributions of the susceptible and infected populations.

We consider the infection rate that can be represented as

\[
\lambda(t,a) = \int_{a_0}^{\infty} \beta(a,a')\pi(t,a,a') \frac{I(t,a')}{N(t,a')} da',
\]
with the total sexually active population given by
\[ N(t, a) = S(t, a) + I(t, a). \]

Here \( \beta(a, a') \) is the probability that an infected partner of age \( a' \) will infect a susceptible partner of age \( a \) during their partnership, \( \pi(t, a, a') \) the rate of pair formation between individuals of age \( a \) and individuals of age \( a' \), and \( I/N \) is the probability that a randomly selected partner is infected.

We assume that the transmission probability is the product of the susceptibility of the susceptible individual and the infectiousness of the infected individual. They can also both depend on age. However, in order to keep the analysis of the model tractable, we allow susceptibility to be age-dependent, but make the somewhat restricting assumption that infectiousness is age-independent. Hence, \( \beta(a, a') = \beta(a) \).

In order to simplify the analysis, we assume that there are no strong biases at work and partners are chosen at random, according to their availability. The random partner selection process leads to a proportionate mixing rate \( \pi \) with the form
\[
\pi(t, a, a') = \frac{r(a)r(a')N(t, a')}{\int_{a_0}^{\infty} r(z)N(t, z) \, dz},
\]
where \( r(a) \) is the partner acquisition rate of individuals of age \( a \), or the number of contacts per individual of age \( a \) per unit of time.

Under these assumptions, the infection rate is
\[
\lambda(t, a) = \beta(a)r(a) \left( \int_{a_0}^{\infty} \frac{r(a')I(t, a')}{\int_{a_0}^{\infty} r(z)N(t, z) \, dz} \, da' \right).
\]

Using the same technique for showing (2.7), we can define the reproductive number for model (4.1) with (4.2) as
\[
R_0 = \frac{\int_{a_0}^{\infty} r(a) \int_{a_0}^{a} \beta(\eta)r(\eta) \exp\{-\int_{\eta}^{a} (\mu(x) + \gamma(x)) \, dx\} S^0(\eta) \, d\eta \, da}{\int_{a_0}^{\infty} r(a) S^0(a) \, da},
\]
where
\[
S^0(a) = Be^{-M(a)} + e^{-M(a)} \int_{a_0}^{a} e^{M(x)} A(x) \, dx,
\]
and
\[
M(a) = \int_{a_0}^{a} \mu(s) \, ds.
\]

By interchanging the order of the integration, \( R_0 \) can also be expressed as
\[
R_0 = \frac{\int_{a_0}^{\infty} r(\eta)S^0(\eta)\beta(\eta) \int_{\eta}^{\infty} r(a) \exp\{-\int_{\eta}^{a} (\mu(x) + \gamma(x)) \, dx\} \, da \, d\eta}{\int_{a_0}^{\infty} r(a) S^0(a) \, da}.
\]

Note that \( \exp\{-\int_{\eta}^{a} (\mu(s) + \gamma(s)) \, ds\} \) is the probability that an individual who is infected at age \( \eta \) is still in the infected population at age \( a \). Then, \( r(a) \exp\{-\int_{\eta}^{a} (\mu(s) + \gamma(s)) \, ds\} \) is the number of
contacts from partners who are infected at age $\eta$ and survive to age $a$, and the total contacts inducing transmission from all surviving infected individuals of all ages $a \geq \eta$ is
\[
\int_{\eta}^{\infty} r(u) \exp \left\{ - \int_{\eta}^{u} (\mu(s) + \gamma(s)) \, ds \right\} \, du.
\]
Again, since $\exp \left\{ - \int_{\eta}^{u} (\mu(s) + \gamma(s)) \, ds \right\}$ is the probability of infected individuals who are infected at age $\eta$ and survive to age $u$, the mean duration of infections of the cohort of age $\eta$ can be expressed as
\[
\bar{\tau}(\eta) \overset{\text{def}}{=} \int_{\eta}^{\infty} \exp \left\{ - \int_{\eta}^{u} (\mu(s) + \gamma(s)) \, ds \right\} \, du.
\]
Then the mean contact rate of the cohort of age $\eta$ can be defined by
\[
\bar{r}(\eta) \overset{\text{def}}{=} \frac{1}{\bar{\tau}(\eta)} \int_{\eta}^{\infty} r(u) \exp \left\{ - \int_{\eta}^{u} (\mu(s) + \gamma(s)) \, ds \right\} \, du.
\]
Define the reproductive number of the cohort of age $\eta$ by
\[
R_0(\eta) \overset{\text{def}}{=} \bar{r}(\eta) \beta(\eta) \bar{\tau}(\eta).
\]
Then the reproductive number for the total population is the infinite sum of the reproductive numbers of all cohorts weighted by the fractions of the total contacts of the cohorts at the infection-free equilibrium, where the reproductive number or the initial transmission is determined; that is,
\[
R_0 = \int_{a_0}^{\infty} \frac{r(\eta)S^0(\eta)}{\int_{a_0}^{\infty} r(a)S^0(a) \, da} R_0(\eta) \, d\eta.
\]

5. Discussion

The reproductive number $R_0$ is one of the most important concepts in epidemiological theory. It characterizes the threshold behavior such that if $R_0 < 1$, the modeled disease will die out if a small number of infected individuals are introduced into a susceptible population, and if $R_0 > 1$, the disease will spread in the population. A good estimate of the reproductive number can provide significant insight into the transmission dynamics of the disease and can lead to effective strategies to control and eventually eradicate the disease.

Formulas (1.1) and (1.2) are useful estimates. They have been applied to various models for different purposes and, in particular, have been widely used in biology and the medical community. Their contributions are significant. For example, sensitive studies of those estimates on different parameters have been used to investigate the effects of changes in sexual behavior on the transmission dynamics of STDs such as HIV [7,31,38]. It was shown in [31] that, in a preferred mixing, single-sex model, reductions in the frequency of partner change by low-activity people can increase the long-term prevalence of HIV/AIDS in populations that would have low steady-state prevalence given current activity levels. Such findings can be used to plan educational campaigns. Formulas for $R_0$ can also be used to establish effective vaccination programs [2,13–16,22]. Effects of different vaccination programs on $R_0$ are useful in setting the programs.
For simple homogeneous models, it is easy to estimate the mean duration, mean number of contacts, and transmission probability so that formulas (1.1) and (1.2) can be applied. As shown in Section 2, it seems that if there is no risk structure involved in the model, no moments higher than the first will be needed in the formula for the reproductive number. More specifically, if the susceptible population is not divided into risk groups, the reproductive number is always based on the first moments. Hence, it should be possible to define the mean number of contacts, the mean duration of infection, and the mean transmission probability in appropriate ways and then \( R_0 \) can be estimated with an intuitive formula. Even if there are subgroups in the infected population with different contact rates, this still seems true. That is, the heterogeneity of the infected population may not be as crucial as that of the susceptible population. This observation can be explained as follows. From the biological point of view, the reproductive number characterizes the situation where a small number of infected individuals are first introduced into an entirely susceptible population. Hence, the heterogeneous structure of the infected population will not play a critical role in the transmission dynamics, at least at the early stage of the transmission. From the mathematical modeling perspective, \( R_0 \) is determined by the stability of the infection-free equilibrium for which the components of infected individuals are 0. Therefore, the heterogeneity of the infected individuals is negligible.

On the other hand, if there is heterogeneous structure in the susceptible population concerned, this heterogeneity cannot be neglected. If an explicit formula of \( R_0 \) can be obtained, higher moments will be naturally involved, and it may be necessary to include the variance or deviation. That is, for different models, although those means may be defined in the same way, their heterogeneous difference may cause significant deviation about the means and then may lead to very different transmission dynamics.

Ideally, appropriate definitions of the means and their variances for the total population can be defined. However, as shown in Sections 3 and 4, if more heterogeneous structures are included in the model, it may not be possible to define those means in practice. More importantly, the deviations from the means have to be taken into consideration. Then it will be more reasonable and practical to define the reproductive number for each structured subgroup or cohort and then use the average of these reproductive numbers weighted by their heterogeneity to estimate the reproductive number for the total population. Heathcote and Yorke [23] and Jacquez et al. [28,29] introduced this idea for risk-group models. Our studies in Sections 3 and 4 support and generalize this idea.

Finally, it is worthwhile to point out from the study of the DS model in Section 2.3 that, although there seems to be heterogeneous structure in the susceptible population for the DS model, since the infection transmission has to be through contacts with infected individuals, and there is only one infected group, higher moments do not appear in this particular situation.

**Acknowledgements**

The authors would like to thank Ann Stanley for leading them in seeking this general formulation of the reproductive number and for her insightful comments and contributions in defining the reproductive number for the DI and SP models. They are also very grateful for Herbert Hethcote for his careful reading throughout the manuscript and valuable comments. This research was supported by the Department of Energy under contracts W-7405-ENG-36 and the Applied Mathematical Sciences Program KC-07-01-01.
Appendix A. Derivation of formula (2.7)

Let \( x = S - S^0 \) and \( y = I \). Then

\[
\dot{x} = r(0) \int_0^\infty \frac{\beta(u) r(u) y(t, u)}{r(0)(x + S^0) + \int_0^\infty r(v) y(t, v) \, dv} \, du \approx \frac{1}{S^0} \int_0^\infty \beta(u) r(u) y(t, u) \, du,
\]

and the linearization of (2.5) about the infection-free equilibrium is given by

\[
\frac{dx}{dt} = -\mu x - \int_0^\infty \beta(u) r(u) y(t, u) \, du,
\]

\[
\frac{\partial y}{\partial t} + \frac{\partial y}{\partial u} = -(\mu + \gamma(u)) y,
\]

\[
y(t, 0) = \int_0^\infty \beta(u) r(u) y(t, u) \, du.
\]

Substituting \( x = x(0)e^{\rho t} \) and \( y = k(u)e^{\rho t} \) into (A.1) yields the following system of equations:

\[
(\rho + \mu)x(0) = -\int_0^\infty \beta(u) r(u) k(u) \, du,
\]

\[
\frac{dk}{du} = -(\rho + \mu + \gamma(u)) k(u),
\]

\[
k(0) = \int_0^\infty \beta(u) r(u) k(u) \, du.
\]

Solving Eq. (A.3) for \( k(u) \) and employing the initial condition (A.4) leads to the following characteristic equation:

\[
\int_0^\infty \beta(u) r(u) \exp \left\{ -\int_0^u (\rho + \mu + \gamma(v)) \, dv \right\} \, du = 1.
\]

Then, it is easy to see if \( R_0 < 1 \), all roots \( \rho \) of (A.5) have negative real part, and if \( R_0 > 1 \), there exists at least one positive root \( \rho \) of (A.5).

Appendix B. Derivation of formula (2.12)

The Jacobian at an equilibrium has the form

\[
\begin{pmatrix}
M & \cdot \\
0 & D
\end{pmatrix},
\]

where \( M = \text{diag}(-\mu, \ldots, -\mu) \) and
evaluated at the infection-free equilibrium with \( \sigma_i \equiv \mu + v_i \).

Set \( Q_i = 1/N^0 \sum_{k=1}^n p_k S^0_k z_k, \ i = 1, \ldots, m, \) with \( N^0 = \sum_{i=1}^n S^0_i \). Then \( D \) has the form of

\[
D = \begin{pmatrix}
-\sigma_1 + \sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_1} & \sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_2} & \cdots & \sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_m} \\
\sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_1} & -\sigma_2 + \sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_2} & \cdots & \sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_m} \\
\vdots & \vdots & \ddots & \vdots \\
\sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_1} & \sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_2} & \cdots & -\sigma_m + \sum_{k=1}^n p_k S^0_k \frac{\partial \beta_k}{\partial I_m}
\end{pmatrix}
\]

Consider \(-D\) and let \( V \equiv (1/\sigma_1, \ldots, 1/\sigma_m) \). Then

\[
-DV = \left( 1 - \sum_{i=1}^m r_i Q_i \frac{\beta_i}{\sigma_i} \right) E,
\]

where \( E \) is the vector each of whose elements is one. Let \( R_0 \equiv \sum_{i=1}^m r_i Q_i \beta_i / \sigma_i \). Then, from M-matrix theory, all eigenvalues of \( D \) have negative real part if \( R_0 < 1 \) which leads to the local stability of the infection-free equilibrium. On the other hand, by mathematical induction, it can be shown that the determinant of \( D \) is given by

\[
\det D = (-1)^{m+1} \prod_{i=1}^m \sigma_i (R_0 - 1).
\]

Hence, if \( R_0 > 1 \), \( D \) has at least one positive eigenvalue. Therefore, the reproductive number for the model (2.10) can be defined as

\[
R_0 = \frac{1}{N^0} \sum_{i=1}^m \sum_{k=1}^n \frac{p_k S^0_k r_i \beta_i}{\mu + v_i}.
\]

**Appendix C. Derivation of formula (3.3)**

The Jacobian matrix at the infection-free equilibrium \( (S_1 = S^0_1, \ldots, S_n = S^0_n, I^1_1 = 0, I^1_2 = 0, \ldots, I^1_m = 0, \ldots, I^n_1 = 0, \ldots, I^n_m = 0) \) has the following form:

\[
\begin{pmatrix}
M & \cdot \\
0 & B
\end{pmatrix},
\]

where \( M = \text{diag}(-\mu, \ldots, -\mu) \) and

...
\[
B \overset{\text{def}}{=} \begin{pmatrix}
B_{11} & B_{12} & \cdots & B_{1n} \\
B_{21} & B_{22} & \cdots & B_{2n} \\
\vdots & \vdots & \ddots & \vdots \\
B_{n1} & B_{n2} & \cdots & B_{nn}
\end{pmatrix},
\]

with
\[
B_{ii} \overset{\text{def}}{=} \begin{pmatrix}
a_1^i (r_i \beta_1 - \xi_1^i) & a_1^i r_i \beta_2 & \cdots & a_1^i r_i \beta_m \\
a_2^i r_i \beta_1 & a_2^i (r_i \beta_2 - \xi_2^i) & \cdots & a_2^i r_i \beta_m \\
\vdots & \vdots & \ddots & \vdots \\
a_m^i r_i \beta_1 & a_m^i r_i \beta_2 & \cdots & a_m^i (r_i \beta_m - \xi_m^i)
\end{pmatrix},
\]

and
\[
B_{ij} \overset{\text{def}}{=} \begin{pmatrix}
a_1^i r_j \beta_1 & \cdots & a_1^i r_j \beta_m \\
\vdots & \ddots & \vdots \\
a_m^i r_j \beta_1 & \cdots & a_m^i r_j \beta_m
\end{pmatrix}, \quad i \neq j.
\]

Here, we write
\[
d_j \overset{\text{def}}{=} \frac{p_j r_j S_i^0}{\sum_{k=1}^n r_k S_i^0} \quad \text{and} \quad \xi_j \overset{\text{def}}{=} \frac{\mu + v_j^i}{a_j^i}.
\]

The stability of the Jacobian matrix at the infection-free equilibrium is completely determined by the stability of \( B \). Note that all off-diagonal elements of \( B \) are positive. We consider \(-B\) and take
\[
V \overset{\text{def}}{=} \begin{pmatrix}
\frac{1}{\xi_1^1}, & \cdots, & \frac{1}{\xi_n^1} \\
\frac{1}{\xi_1^n}, & \cdots, & \frac{1}{\xi_n^n}
\end{pmatrix}^T.
\]

Since
\[
-BV = \left(1 - \sum_{k=1}^n \sum_{l=1}^m \frac{r_k \beta_1}{\xi_l} \right) E,
\]

where
\[
E \overset{\text{def}}{=} (a_1^1, \ldots, a_m^1, \ldots, a_1^n, \ldots, a_m^n)^T,
\]

if we define
\[
R_0 \overset{\text{def}}{=} \sum_{k=1}^n \sum_{l=1}^m \frac{r_k \beta_1}{\xi_l} = \sum_{l=1}^n \frac{r_l^2 S_i^0}{\sum_{l=1}^n r_l S_i^0} \sum_{j=1}^n \frac{p_j \beta_j}{\mu + v_j^i},
\]

then it follows from M-matrix theory that \( B \) is stable if \( R_0 < 1 \).
On the other hand, by mathematical induction, it can be shown that the determinant of $B$ is
\[
\det B = (-1)^{nm} \left( \prod_{i=1}^{n} \prod_{j=1}^{m} a_i^j r_i \beta_j \right) \left( \prod_{k=1}^{n} \prod_{l=1}^{m} z_k l \right) \left( 1 - \sum_{k=1}^{n} \sum_{l=1}^{m} \frac{r_k \beta_l}{z_k l} \right)
\]
\[
= (-1)^{nm} \prod_{i=1}^{n} \prod_{j=1}^{m} \left( \mu + v_j \right) (1 - R_0).
\]

Hence, if $R_0 > 1$, matrix $B$ has at least one positive eigenvalue. Therefore, the infection-free equilibrium is unstable.

References