

## AN EPIDEMIC MODEL STRUCTURED BY HOST IMMUNITY

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In this paper we introduce a physiologically structured SIR epidemic model where the individuals are distributed according to their immune status. An individual immune status is assumed to increase during the infectious period and remain unchanged after the recovery. Recovered individuals can become reinfected at a rate which is a decreasing function of their immune status. We find that the possibility of reinfection of recovered individuals results in subthreshold endemic equilibria. The differential immunity of the infectious individuals leads to multiple nontrivial equilibria in the superthreshold case. We present an example that has exactly three nontrivial equilibria. We also analyze the local stability of equilibria.

*Keywords:* Physiological Structure; Immune Status; Reinfection; Immunoepidemiology; Subthreshold Equilibria; Multiple Endemic Superthreshold Equilibria.

### 1. Introduction

Undoubtedly there is a close link between the within-host progression of an infection leading to certain associated immunity and the development of the disease on epidemiological level. Traditionally, mathematical modeling of the immunological response and the epidemiology of a disease have been separated. On the one hand, a substantial amount of literature exists on the within-host immune response to a pathogen (see Nowak and May<sup>1</sup> and the references therein). On the other hand, a number of articles discuss the spread of diseases on a population level (see Hethcote<sup>2</sup> and the references therein). The immune status of the hosts, however, their level of innate, naturally and/or artificially acquired immunity, has a significant impact on the spread of an infectious disease in a population. In the classical epidemiological approach, the variability of host parasite-specific immunity and cross-immunity is incorporated in epidemic models by subdividing the entire population of hosts into various subclasses corresponding to different levels of immune protection — naive

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or completely susceptible, completely or partially immune, vaccinated, etc. To capture a complex immune structure of the disease-affected individuals, some models incorporate  $n$  recovered classes.<sup>3,4</sup> Epidemic models of the intricate interdependence between the influenza virus and the host immune system involve multiple strains and recovered classes that include individuals immune to various combinations of the influenza strains.<sup>5,6</sup> Although incorporating immunological concepts in epidemic models is not new, it is often accomplished through incorporation of more classes which increases the complexity of the model.

The immunological models describing the within-host dynamics of the pathogens and the respective immune responses are typically “self-contained” and the interdependence with the epidemiology of the disease, if it exists, is mostly implicit.<sup>7–10</sup> These models typically describe the dynamics of a single infection where the initial pathogenic load and the immune status of the host are assigned somewhat arbitrarily. Even when the immunological dynamics is linked to various epidemiological parameters, most often transmission,<sup>11–17</sup> there is no explicit account for the immune memory developed through prior exposures to the pathogen. Such phenomena as reinfection or superinfection can be factored into the dynamics via resetting the pathogenic load at some specified time points, but these perturbations do not depend on the population contact rate or the distribution of the infectious individuals in the entire population of hosts.

Bridging the gap between immunology and epidemiology in theory and empirical studies is at the heart of the emerging discipline of immunoepidemiology.<sup>18</sup> Mathematical models at this interface have been formulated mostly in relation to macroparasitic diseases. For instance, they have been used to address the question whether different parasite load in helminth infection is a result of discrepancies in the contact rates or of the acquired immunity<sup>19</sup> or simply to account for the effect of acquired immunity on the epidemiology of the disease.<sup>20</sup>

Immunoepidemiological models can provide a deeper understanding of the coevolution of the pathogen and its host. They can naturally account for the selective pressure on the parasite exhibited by the host’s immune system<sup>21</sup> that tends to increase the parasites’ fitness by optimizing the reproduction number of the disease on population level.<sup>14</sup> This allows for a more general interpretation of the parasite fitness compared to the traditional strictly within-host case.<sup>22</sup> Epidemiological and immunological models seem to have been first considered in parallel in Anderson.<sup>23</sup> A nested approach where the epidemiology of the disease is modeled with age-since-infection SIR model while the immunology on individual level is described by a simple predator-prey type model for the pathogen and the immune response cells is employed in Gilchrist and Sasaki.<sup>14</sup> The dynamics at both levels are linked through epidemiological parameters related to the within-host variables.

Another interesting question in immunoepidemiology is to understand the relation between the dynamics of recurrent diseases and the dynamic variability of the

acquired immunity to these diseases within the host population. In case of malaria, the acquired immunity is exposure-dependent, i.e. malaria-specific immunity is boosted upon each exposure and it gradually declines between the consecutive bouts of the disease.<sup>24–26</sup> Modeling the dynamics of the distribution of humans with regard to their immune status becomes a critical step in controlling the prevalence of malaria and designing appropriate vaccination strategies. Considering the immune structure of the host population has a potential of explaining important epidemiological patterns, such as multiple stable immunological patterns, and nontrivial relations between the disease prevalence and the disease transmission levels.<sup>27,28</sup> Bistable distributional patterns have been previously reported in a physiologically structured model of cannibalistic fish.<sup>29</sup> There the ecological mechanism responsible for this dynamical behavior is the energy gain from cannibalism. The authors refer to it as the “Hensel and Gretel” effect. In the present report, we argue that the host population structured with respect to the immune status may also exhibit multistable distributional patterns.

In this paper we use a mathematical model of physiologically structured type to provide the link between the epidemiology of the disease and the immune status of the individuals in the population. Our model is in the form of partial differential equation as opposed to the integral equation approach developed.<sup>30,31</sup> Physiologically structured models have been used to model size-structured populations<sup>32–34</sup> and metapopulations.<sup>35</sup>

This paper is organized as follows. In the next section we introduce an SIR-type epidemic model structured by the immune status of the individuals. In Sec. 3, we investigate the equilibria of the model. We establish criteria for subthreshold existence of nontrivial equilibria. We also show that in some cases multiple superthreshold equilibria exist. In Sec. 4, we investigate the local stability of equilibria. In Sec. 5, we present the dynamics of the unstructured model which is an SIR model where the recovered individuals can get reinfected. In Sec. 6, we summarize our findings and give conclusions.

## 2. Model Formulation

We consider a model which takes into account the immune status of the individuals. Individuals who are healthy, have not been previously exposed to the infection, and have no immunity to the disease form the susceptible class. The number of individuals in the susceptible class at time  $t$  is given by  $S(t)$ . A typical within-host dynamics of an acute infection consists of three major phases: (1) a rapid pathogen growth followed by the rise of the specific immunity, (2) control of the pathogen by immunity, and (3) clearance of the pathogen and generation of immune memory.<sup>36</sup> For the purpose of this paper, we assume that individuals who are infected mount a specific immune response and simultaneously start developing a long-term infection-specific immune memory. We will denote by  $x$  the level of protective immunity

which is positively correlated with the number<sup>a</sup> of memory T cells specific to a given antigen that an individual has. We will refer to  $x$  as the *immune status* of a given individual. The density of infected individuals with immune status  $x$  at time  $t$  is given by  $i(x, t)$ . According to our assumptions, the immune status  $x$  increases over the course of infection. We model the rate of increase of the immune status by introducing a function  $g(x)$  such that the immune status of any given individual satisfies the following ordinary differential equation

$$x' = g(x)$$

where the initial status is some given quantity  $x(0) = x_0$ . We have that  $g(x) > 0$  for all  $x \geq 0$  which reflects our assumption that the immune status increases. This assumption is acceptable in mathematical modeling and has been used on several occasions before.<sup>11,14</sup>

We denote (see Table 1) by  $\beta$  the contact rate for susceptible individuals and with  $h(x)$  the probability density that transmission of the disease occurs given a contact between a susceptible and an infective of immune status  $x$ . Thus, the infectivity of infected individuals is a certain function of their immune status and we denote this function by  $\beta h(x) \geq 0$ . The function  $h(x)$  is assumed bounded and integrable. A susceptible individual can be infected by an infectious individual with any immune status at a rate

$$\beta \frac{S(t)}{N(t)} \int_0^\infty h(x)i(x, t) dx,$$

where  $N(t)$  is the total number of individuals in the population. We will use the notation

$$H(t) = \int_0^\infty h(x)i(x, t) dx$$

Table 1. List of parameters.

Notation	Meaning
$\Lambda$	Birth/recruitment rate into the population
$\mu$	Per capita natural death rate
$\beta$	Contact rate for susceptible individuals
$h(x)$	Infectiousness of infective individuals with immune status $x$
$\rho(x)$	Reinfection rate
$\gamma(x)$	Recovery rate of infectious individuals
$\nu(x)$	Disease-induced mortality
$g(x)$	Rate of increase of immune status during infection
$d(x)$	Rate of decrease of immune status while recovered

<sup>a</sup>We should point out that the total number of antigen-specific immune cells, or simply the immune memory load, need not be exactly the same as the immune status. For instance, in a biologically plausible scenario, the immune memory load can be a saturating function of the immune status reflecting the fact that above a certain threshold, the number of memory cells may provide a complete protection against subsequent infections with the same pathogen.

to denote the total infectiousness of all infectious individuals with any immune status. With this notation the force of infection is given by  $\beta H(t)/N(t)$ . We note that the force of infection is of proportionate mixing type which some authors believe is most appropriate for modeling the spread of STDs.<sup>37</sup> Upon infection, a susceptible individual enters the infectious class with zero immune status ( $\bar{x} = 0$ ). Infectious individuals recover at a rate  $\gamma(x)$  and move to the recovery class  $r(x, t)$ . The immune status in recovered individuals may decline at a rate  $d(x)$  according to the law

$$x' = -d(x).$$

Recovered individuals can be reinfected at a rate  $\rho(x)$  which depends on their immune status  $x$ . Finally, we assume that  $\rho(x)$  is a decreasing function of  $x$  with  $\rho(x) < \beta h(x)$ . Upon reinfection, individuals return to the infectious class and enter it at the same immune status level as they had in the recovered class. We arrive at the following model (see Fig. 1).

$$\begin{aligned} S'(t) &= \Lambda - \beta \frac{H(t)}{N(t)} S - \mu S + d(0)r(0, t) \\ i_t(x, t) + (g(x)i(x, t))_x &= \rho(x) \frac{H(t)}{N(t)} r(x, t) - (\gamma(x) + \mu + \nu(x))i(x, t) \\ g(0)i(0, t) &= \beta \frac{H(t)}{N(t)} S(t) \\ r_t - (d(x)r(x, t))_x &= -\rho(x) \frac{H(t)}{N(t)} r(x, t) + \gamma(x)i(x, t) - \mu r(x, t) \end{aligned} \tag{2.1}$$

where the total population size  $N$  is the sum of the susceptible ( $S$ ) total infectious ( $I$ ) and total recovered ( $R$ ) populations:  $N(t) = S(t) + I(t) + R(t)$ , where

$$I(t) = \int_0^\infty i(x, t) dx \quad R(t) = \int_0^\infty r(x, t) dx.$$

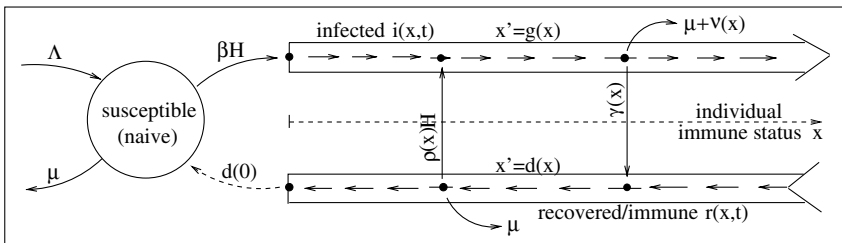


Fig. 1. The flow diagram of the model. Any individual lacking immunity against the infection is considered susceptible (or naive). The immune status of infected individuals increases with time spent in the infected class at the rate  $x' = g(x) > 0$ . Infected individuals with immune status  $x$  recover at the rate  $r(x)$  and enter the recovered class. The immune status of recovered individuals declines with time at the rate  $x' = -d(x) \leq 0$ . Recovered individuals with immune status  $x \leq 0$  are treated as susceptible (or naive). The rate of infection is denoted as  $\beta H$  and the rate of reinfection is denoted as  $\rho(x)H$ . The terms  $\Lambda$ ,  $\mu$ , and  $\nu(x)$  represent the rates of birth, natural mortality, and disease-associated mortality.

The total population satisfies the differential equation which is obtained by adding all equations in (2.1)

$$N'(t) = \Lambda - \mu N - \int_0^\infty \nu(x)i(x, t)dx.$$

The second equation in (2.2) governs the dynamics of the distribution of infected individuals with respect to their immune status. Neglecting the interior sources and removal of individuals from the infected class, the number of infected individuals with immune statuses anywhere between  $x_1$  and  $x_2$  ( $0 \leq x_1 < x_2$ ) changes according to the equation

$$\frac{d}{dt} \int_{x_1}^{x_2} i(x, t) dx = g(x_1)i(x_1, t) - g(x_2)i(x_2, t),$$

where the term  $g(x)i(x, t)$  represents the flux through the boundary into the infected class. Using the Fundamental Theorem of Calculus and the fact that  $x_1$  and  $x_2$  are arbitrary, the above equation can be rewritten in the transport form  $i_t(x, t) + (g(x)i(x, t))_x = 0$ , which is the left-hand side of the equation for the density of infectives in (2.2). The right-hand side of the same equation represents the sum of all the sources and the sinks. The boundary condition relates the influx  $g(0)i(0, t)$  to the rate at which susceptible individuals become infected. The equation governing the dynamics in the recovered class is derived similarly.

In the remainder of this article, we will consider as a starting point only the case when the immune status remains constant after recovery, i.e. we will assume that  $d(x) = 0$ . We will also take  $\nu(x) = 0$ . The case when  $\nu(x) \neq 0$  leads to the same conclusions as the case  $\nu = 0$  but with more complex formulas. With these assumptions, the model that we consider is:

$$\begin{aligned} S'(t) &= \Lambda - \beta \frac{H(t)}{N(t)} S - \mu S \\ i_t(x, t) + (g(x)i(x, t))_x &= \rho(x) \frac{H(t)}{N(t)} r(x, t) - (\gamma(x) + \mu)i(x, t) \\ g(0)i(0, t) &= \beta \frac{H(t)}{N(t)} S(t) \\ r_t &= -\rho(x) \frac{H(t)}{N(t)} r(x, t) + \gamma(x)i(x, t) - \mu r(x, t). \end{aligned} \tag{2.2}$$

In the case when the disease-induced mortality is zero  $\nu = 0$ , the total population is asymptotically constant  $N(t) \rightarrow \frac{\Lambda}{\mu}$ . That allows us to reduce the system (2.2) to the invariant set  $N = N^* = \frac{\Lambda}{\mu}$ , to obtain

$$\begin{aligned} s'(t) &= \mu - \beta J(t)s(t) - \mu s(t) \\ j_t(x, t) + (g(x)j(x, t))_x &= \rho(x)J(t)u(x, t) - (\gamma(x) + \mu)j(x, t) \\ g(0)j(0, t) &= \beta J(t)s(t) \\ u_t(x, t) &= -\rho(x)J(t)u(x, t) + \gamma(x)j(x, t) - \mu u(x, t), \end{aligned} \tag{2.3}$$

where

$$s(t) = \frac{S(t)}{N^*} \quad j(x, t) = \frac{i(x, t)}{N^*} \quad u(x, t) = \frac{r(x, t)}{N^*}$$

are the proportions of susceptible, infectious and recovered individuals, and  $J(t) = \frac{H(t)}{N^*} = \int_0^\infty h(x)j(x, t) dx$ .

The model (2.2) is a classical SIR model which allows for further infection of recovered individuals. It models adequately all diseases where individuals recover but can be infected repeatedly, such as influenza (if we take a macro-viewpoint of it and consider all strains indistinguishable), tuberculosis, gastroenteritis or “stomach flu,” some STDs and others.

### 3. Equilibria

The long-term behavior of solutions is determined in part by the equilibria that are time-independent solutions of the system (2.2). Let  $s, j(x)$  and  $u(x)$  be the proportions of susceptible, infectious and recovered individuals at equilibrium, and  $J = \frac{H}{N^*} = \int_0^\infty h(x)j(x) dx$ . Replacing all time derivatives in (2.2) by zeroes, and dividing through by  $N^*$  we find that the equilibria satisfy the equations:

$$\begin{aligned} 0 &= \mu - \beta J s - \mu s \\ (g(x)j)_x &= \rho(x)J u(x) - (\gamma(x) + \mu)j(x) \\ g(0)j(0) &= \beta J s \\ 0 &= -\rho(x)J u(x) + \gamma(x)j(x) - \mu u(x). \end{aligned} \tag{3.1}$$

From the last equation in (3.1), we have

$$u(x) = \frac{\gamma(x)j(x)}{\rho(x)J + \mu}. \tag{3.2}$$

Substituting (3.2) in the second equation of (3.1) and integrating, we obtain

$$g(x)j(x) = \beta J s e^{-\mu \int_0^x \frac{\gamma(\sigma)}{g(\sigma)[\rho(\sigma)J + \mu]} d\sigma} e^{-\mu \int_0^x \frac{1}{g(\sigma)} d\sigma} \tag{3.3}$$

where from the first equation we have the value of  $s$  in terms of  $J$ :

$$s = \frac{\mu}{\beta J + \mu}. \tag{3.4}$$

From the equation above it is clear that  $s \leq 1$  and it is defined for every  $J \geq 0$ . The expressions for  $j(x)$  and  $u(x)$  are also well defined and it is easy to see that  $\int_0^\infty j(x) dx \leq 1$  and  $\int_0^\infty u(x) dx \leq 1$ , since

$$s + \int_0^\infty j(x) dx + \int_0^\infty u(x) dx = 1.$$

The system (2.2) always admits the unique disease-free equilibrium

$$\mathcal{E}_0 = (1, 0, 0)$$

where the entire population consists of susceptibles. Nontrivial equilibria are obtained if a value of  $J > 0$  is known and substituted in expressions (3.2)–(3.4) for  $s$ ,  $j(x)$  and  $u(x)$ . The equilibrium values for  $J$  are positive roots of the equation which is obtained by substituting the right-hand side of (3.3) into the formula for  $J$  and dividing both sides by  $J$ :

$$\frac{\beta\mu}{\beta J + \mu} \eta(J) = 1 \tag{3.5}$$

where  $\eta(J)$  denotes the integral

$$\eta(J) = \int_0^\infty \frac{h(x)}{g(x)} e^{-\mu \int_0^x \frac{\gamma(\sigma)}{g(\sigma)[\rho(\sigma)J + \mu]} d\sigma} e^{-\mu \int_0^x \frac{1}{g(\sigma)} d\sigma} d\sigma. \tag{3.6}$$

The left-hand side of Eq. (3.5) is a function of  $J$ . We denote that function by  $R(J)$  and we plot it in Fig. 2. Equilibrium values for  $J$  are given by the points where this function crosses the horizontal axis — there are three of them in Fig. 2.

Each positive root  $J^*$  of Eq. (3.5) corresponds to a nontrivial equilibrium  $\mathcal{E}^* = (s^*, j^*(x), u^*(x))$ . The number of roots of Eq. (3.5) gives the number of nontrivial equilibria of the system (2.2). The number of equilibria is determined by the specific immune status structure and the reproduction number of the disease. The reproduction number is given by

$$\mathcal{R}_0 = \beta \int_0^\infty \frac{h(x)}{g(x)} e^{-\int_0^x \frac{\gamma(\sigma)}{g(\sigma)} d\sigma} e^{-\mu \int_0^x \frac{1}{g(\sigma)} d\sigma} d\sigma.$$

The reproduction number gives the number of secondary infections one infectious individual will produce while being infectious in an entirely susceptible population. The term  $e^{-\mu \int_0^x \frac{1}{g(\sigma)} d\sigma}$  gives the probability of surviving to immune status  $x$ , the term  $e^{-\int_0^x \frac{\gamma(\sigma)}{g(\sigma)} d\sigma}$  gives the probability of still being infective, and  $\beta h(x)$  gives the secondary infections produced at immune status  $x$ . The integral accumulates all those quantities for all immune statuses. We note that  $\mathcal{R}_0 = \beta\eta(0)$  does not depend

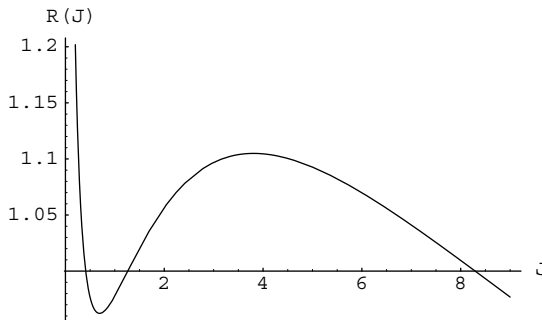


Fig. 2. The graph of the function  $R(J)$  is given with  $h(x) = hx$  where  $h = 2$ . The values of the remaining constant parameters are  $\beta = 15$ ,  $g = 5.5$ ,  $\mu = 0.5$ ,  $\gamma = 5.5$ ,  $\rho = 1$ . The value of the reproduction number in this case is  $\mathcal{R}_0 = 4.58333$ . The graph shows that the equation  $R(J) = 1$  has three positive solutions.



on the reinfection rate  $\rho$  since reinfection does not lead to infections of susceptible individuals. In what follows, we order the nontrivial equilibria according to the corresponding values of  $J$ . In particular, we will say that  $\mathcal{E}^* \leq \mathcal{E}^{**}$  if  $J^* \leq J^{**}$ . Considering the number of equilibria, first we notice that since  $\eta(J)$  is an increasing function of  $J$  while  $\frac{1}{\beta J + \mu}$  is a decreasing function, the left-hand side of Eq. (3.5) may be increasing or decreasing which allows the possibility for multiple nontrivial equilibria. We can determine the number of endemic equilibria if they are all simple. We call an equilibrium  $\mathcal{E}^*$  *simple* if  $J$  is a simple root of Eq. (3.5), otherwise we call  $\mathcal{E}^*$  an equilibrium of *high multiplicity*. It can be shown that for almost all values of the reproduction number all roots are simple. Thus for the number of nontrivial equilibria we have the following general result.

**Proposition 3.1.** (a) *If  $\mathcal{R}_0 < 1$  the system (2.2) might or might not have nontrivial equilibria. If all nontrivial equilibria are simple, then their number is even.*

(b) *If  $\mathcal{R}_0 > 1$  then there exists at least one nontrivial equilibrium. If all nontrivial equilibria are simple, then their number is odd.*

**Proof.** To show part (a), we use the notation  $R(J)$  for the left-hand side of (3.5). We note that

$$\lim_{J \rightarrow \infty} \eta(J) = \int_0^\infty \frac{h(x)}{g(x)} e^{-\mu \int_0^x \frac{1}{g(\sigma)} d\sigma} dx < \infty.$$

Hence,  $\lim_{J \rightarrow \infty} R(J) = 0$ . Since  $R(0) = \mathcal{R}_0 < 1$ , the total number of roots of  $R(J) = 1$  counting their multiplicity must be even.<sup>b</sup> If all roots are simple, their number is even. To show (b), we notice that  $R(0) = \mathcal{R}_0 > 1$ . Thus,  $R(J) = 1$  has at least one positive root. If there is more than one — there should be an odd number of them since all solutions are simple — that is, all common points are a result of intersection. This completes the proof.  $\square$

Subthreshold endemic equilibria in the case  $\mathcal{R}_0 < 1$  are typically obtained through backward bifurcation. If the backward bifurcation occurs, there is a range of the reproduction numbers  $\mathcal{R}^* < \mathcal{R}_0 < 1$  for which there are at least two nontrivial equilibria. To derive a necessary and sufficient condition for the backward bifurcation to occur, we treat  $\beta$  as a bifurcation parameter and use (3.5) to express  $\beta$  as a function of  $J$  at equilibrium:

$$\beta(J) = \frac{\mu}{\mu\eta(J) - J}.$$

The bifurcation at the critical value  $\mathcal{R}_0 = 1$  is backward if and only if  $\beta'(0) < 0$ . The last condition is equivalent to the condition  $\mu\eta'(0) > 1$ . Consequently, we have the following criterion.

<sup>b</sup>Since the function  $R(J)$  is analytic in some neighborhood of any positive root of  $R(J) = 1$ , any such root has a finite multiplicity.

**Proposition 3.2.** *The bifurcation is backward if and only if*

$$\mu\eta'(0) > 1. \tag{3.7}$$

*When the bifurcation is backward, the system (2.2) has subthreshold endemic equilibria in some range  $\mathcal{R}^* < \mathcal{R}_0 < 1$ .*

We note that the quantity  $\eta'(0)$  is given by

$$\eta'(0) = \frac{1}{\mu} \int_0^\infty \frac{h(x)}{g(x)} \left( \int_0^x \frac{\gamma(\sigma)\rho(\sigma)}{g(\sigma)} d\sigma \right) e^{-\int_0^x \frac{\gamma(\sigma)}{g(\sigma)} d\sigma} e^{-\mu \int_0^x \frac{1}{g(\sigma)} d\sigma} dx.$$

It is easy to see that inequality (3.7) is nontrivial, i.e., there are parameter values for which it holds. In particular, it holds for sufficiently large values of  $\rho$ . We recall that the reproduction number  $\mathcal{R}_0$  does not depend on  $\rho$  and, consequently, all other parameters can be held fixed so that  $\mathcal{R}_0 < 1$ . The inequality (3.7) will hold even if all parameters are constants. Thus the corresponding ODE model, obtained from (2.2) by taking  $h(x) = h$ ,  $\gamma(x) = \gamma$ ,  $\rho(x) = \rho$  independent of  $x$ , also has subthreshold equilibria. The necessary and sufficient condition (3.7) is clearly not satisfied if  $\rho(x) = 0$  or if  $\gamma(x) = 0$  for all  $x$ . Hence, the mechanisms responsible for the backward bifurcation are reinfection and recovery. From a mathematical point of view inequality (3.7) will not hold if  $h(x) = 0$  for all  $x$  but in this case there will be no infection at all. Thus, the corresponding scenario is rather trivial.

The stability of both trivial and nontrivial equilibria will be investigated in the next section. Here we note that generally speaking there are two kinds of equilibria. We rewrite Eq. (3.5) in the form

$$\beta\mu\eta(J) - \beta J - \mu = 0.$$

We recall that the equilibria are numbered in increasing order of  $J$  and we assume that they are all simple. Each equilibrium corresponds to a root of  $\beta\mu\eta(J) - \beta J - \mu = 0$ . If  $\mathcal{R}_0 > 1$  then at  $J = 0$  we have that  $\beta\mu\eta(0) - \mu > 0$  and at the first intersection and every other intersection the function  $\beta\mu\eta(J) - \beta J - \mu$  changes sign from positive to negative. Thus, at the odd numbered equilibria its slope is negative, that is  $\mu\eta'(J^*) < 1$  which is equivalent to  $R'(J^*) < 0$ . Similarly, with the even number equilibria the function  $\beta\mu\eta(J) - \beta J - \mu$  changes sign from negative to positive. Thus, at the even numbered equilibria it is increasing and its slope is positive,  $\mu\eta'(J) > 1$ . This last inequality is equivalent to  $R'(J^*) > 0$ . The situation is reversed when the inequality  $\mathcal{R}_0 < 1$  holds since  $\beta\mu\eta(0) - \mu < 0$ . Consequently, we have the following result that characterizes the two types of equilibria (see Fig. 2 for the case of multiple equilibria when  $\mathcal{R}_0 > 1$  where for the first and third intersection of the curve with the horizontal axis the slope of the curve at the intersection is negative while at the second intersection the slope of the curve is positive).

**Proposition 3.3.** *Assume all equilibria are simple and ordered in increasing order of  $J$ . If  $\mathcal{R}_0 > 1$  then at every odd numbered equilibrium we have  $\mu\eta'(J) < 1$  ( $R'(J^*) < 0$ ) while at every even numbered equilibrium we have  $\mu\eta'(J) > 1$*

( $R'(J^*) > 0$ ). If  $\mathcal{R}_0 < 1$  then at every odd numbered equilibrium we have  $\mu\eta'(J) > 1$  ( $R'(J^*) > 0$ ) while at every even numbered equilibrium we have  $\mu\eta'(J) < 1$  ( $R'(J^*) < 0$ ).

The immune status structure has significant impact on the number of equilibria. In particular, if there is no immune status structure in the model, i.e. if all coefficients are constant,  $h(x) = h$ ,  $\rho(x) = \rho$ ,  $\gamma(x) = \gamma$  and  $g(x) = g$ , then the Eq. (3.5) takes the form

$$R(J) = \frac{\beta h}{\beta J + \mu} \frac{\rho J + \mu}{\rho J + \mu + \gamma} = 1.$$

This equation is clearly equivalent to a quadratic equation and hence it has at most two positive solutions. We note that with the following values of the parameters  $\beta = 1$ ,  $h = 1.85$ ,  $\mu = 1$ ,  $\gamma = 1$ ,  $\rho = 5$  which satisfy condition (3.7) the equation above has the following two positive solutions:  $J_1^* = 0.0813859$  and  $J_2^* = 0.368614$ . In general in the constant coefficient case, Proposition 3.1 leads to the result.

**Corollary 3.1.** *Suppose that  $h(x) = h$ ,  $\rho(x) = \rho$ ,  $\gamma(x) = \gamma$  and  $g(x) = g$  are all constant. If  $\mathcal{R}_0 < 1$  and there are subthreshold nontrivial equilibria then there are two of them. If  $\mathcal{R}_0 > 1$  then there is always a unique endemic equilibrium.*

The number of endemic equilibria can change significantly when there is an essential dependence on the immune status  $x$ . To illustrate this point, we consider a special case in which all parameters are constant except  $h(x)$ . We allow the infectiousness of infected individuals to vary linearly with their immune status. In particular, we take  $h(x) = hx$  where  $h$  is a constant. This simple dependence leads to another relatively simple form of the equation for  $J$ , namely (3.5) becomes

$$R(J) = \frac{\beta hg}{\mu(\beta J + \mu)} \left( \frac{\rho J + \mu}{\rho J + \mu + \gamma} \right)^2 = 1.$$

This function is plotted in Fig. 2 for some specific values of the constant parameters as given in the figure caption. It is clear from this graph that in the case  $\mathcal{R}_0 > 1$  the equation  $R(J) = 1$  has three positive solutions  $J_1 < J_2 < J_3$  corresponding to three nontrivial equilibria of the system (2.2). We surmise that a more complicated dependence of the parameters on the immune status can potentially lead to more nontrivial equilibria.

#### 4. Local Stability of Equilibria

We denote the first variation of  $s$  by  $\xi$ , of  $i(\cdot)$  by  $y(\cdot)$  and of  $r(\cdot)$  by  $z(\cdot)$ , respectively. In addition, the first variation of  $H(t)$  is denoted by  $\chi(t)$ . Linearizing the system (2.3) around an equilibrium, we obtain a system for the time-dependent variations. To find the eigenvalues  $\lambda$  of the linearized system, we consider first variations of the form  $\xi(t) = e^{\lambda t} \bar{\xi}$ ,  $y(x, t) = e^{\lambda t} \bar{y}(x)$  and  $z(x, t) = e^{\lambda t} \bar{z}(x)$ . Substituting these in

the linearized system of (2.3) we obtain the following linear eigenvalue problem for  $\bar{\xi}$ ,  $\bar{y}(x)$  and  $\bar{z}(x)$ . In the system below we have omitted the bars for simplicity.

$$\begin{aligned}
 \lambda \xi &= -\beta s^* \chi - \beta J^* \xi - \mu \xi \\
 (g(x)y)_x &= -\lambda y + \rho(x)J^*z(x) + \rho(x)u(x)\chi - (\gamma(x) + \mu)y(x) \\
 g(0)y(0) &= \beta s^* \chi + \beta J^* \xi \\
 \lambda z(x) &= -\rho(x)J^*z(x) - \rho(x)u(x)\chi + \gamma(x)y(x) - \mu z(x),
 \end{aligned}
 \tag{4.1}$$

where  $J^* = \frac{H^*}{N^*} = \int_0^\infty h(x)j(x)dx$ . We also have that

$$\chi = \int_0^\infty h(x)y(x)dx.
 \tag{4.2}$$

At the disease-free equilibrium,  $s^* = 1$ ,  $u(x) = 0$ , and  $J^* = 0$ , and the system (4.1) simplifies significantly.

Solving the differential equation and substituting the solution into the formula for  $\chi$  (4.2) we obtain an equation for the eigenvalues  $\lambda$  called the characteristic equation of the disease-free equilibrium. This equation is of the form  $\mathcal{G}(\lambda) = 1$  where

$$\mathcal{G}(\lambda) = \beta \int_0^\infty \frac{h(x)}{g(x)} e^{-(\lambda+\mu) \int_0^x \frac{1}{g(\sigma)} d\sigma} e^{-\int_0^x \frac{\gamma(\sigma)}{g(\sigma)} d\sigma} dx.$$

If all solutions (real and complex) of this equation have negative real parts, then the disease-free equilibrium is locally asymptotically stable, meaning that every solution starting sufficiently close to that equilibrium will approach it in forward time.

To see the location of the solutions of the characteristic equation  $\mathcal{G}(\lambda) = 1$  we observe that  $\mathcal{G}(0) = \mathcal{R}_0$  and, in addition, for real values of  $\lambda$ ,  $\mathcal{G}(\lambda) \rightarrow 0$  as  $\lambda \rightarrow \infty$ . We illustrate the possibilities in Fig. 3. Thus, if  $\mathcal{R}_0 > 1$  then the equation  $\mathcal{G}(\lambda) = 1$  has a positive real solution. Consequently, the disease-free equilibrium is unstable. If, on the other hand,  $\mathcal{R}_0 < 1$  then from Fig. 3 one can see that there are no nonnegative real roots to the characteristic equation. Furthermore, for any

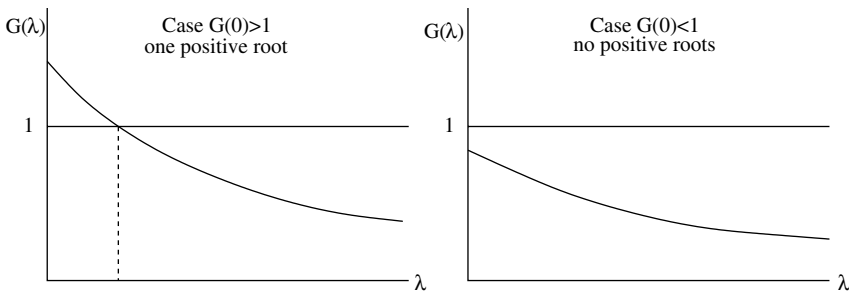


Fig. 3. The graph of the function  $\mathcal{G}(\lambda)$  is given with  $\lambda$  being a real variable. The left figure shows the case when  $\mathcal{G}(0) = \mathcal{R}_0 > 1$ . Then there is a unique positive real root to the equation  $\mathcal{G}(\lambda) = 1$ . The figure on the right shows the case when  $\mathcal{G}(0) = \mathcal{R}_0 < 1$ . Then there are no real nonnegative roots to the equation  $\mathcal{G}(\lambda) = 1$ .

complex  $\lambda$  with  $\Re\lambda \geq 0$  we have that  $|\mathcal{G}(\lambda)| \leq \mathcal{G}(\Re\lambda) \leq \mathcal{G}(0) = \mathcal{R}_0 < 1$ . Therefore, the equation  $\mathcal{G}(\lambda) = 1$  has no solutions with nonnegative real part. This leads to the following traditional result.

**Proposition 4.1.** *If  $\mathcal{R}_0 < 1$  then the disease-free equilibrium is locally asymptotically stable. If  $\mathcal{R}_0 > 1$  then the disease-free equilibrium is unstable.*

To derive the characteristic equation of an endemic equilibrium we consider the full system (4.1). From the last equation we express  $z(x)$  in terms of  $\chi$  and  $y(x)$  and substitute it in the equation for  $y(x)$ . Expressing  $\xi$  from the first equation and substituting it in the initial condition for  $y(x)$  it depends on  $\chi$  and  $\lambda$  only. Solving the differential equation with its initial condition and replacing  $y(x)$  in (4.2) we obtain the characteristic equation  $\mathcal{Q}(\lambda, J^*) = 1$  where  $\mathcal{Q}(\lambda, J^*)$  depends in a complex way on the parameters of the model (2.2) and on a particular solution of the Eq. (3.5) which is denoted by  $J^*$ .

In the previous section we showed that when multiple equilibria are present there are two types of them — equilibria for which  $\mu\eta'(J^*) > 1$ , i.e.  $R'(J^*) > 0$ , and equilibria for which  $\mu\eta'(J^*) < 1$ , i.e.  $R'(J^*) < 0$  (see Fig. 2 for the case  $\mathcal{R}_0 > 1$ ). Now we consider the key element that relates the type of the equilibrium to its stability (see also Fig. 4).

**Proposition 4.2.** *Let  $J^*$  be a solution of the Eq. (3.5). Then*

- (1)  $\mathcal{Q}(0, J^*) < 1$  if and only if  $\mu\eta'(J^*) < 1$  ( $R'(J^*) < 0$ ).
- (2)  $\mathcal{Q}(0, J^*) = 1$  if and only if  $\mu\eta'(J^*) = 1$  ( $R'(J^*) = 0$ ).
- (3)  $\mathcal{Q}(0, J^*) > 1$  if and only if  $\mu\eta'(J^*) > 1$  ( $R'(J^*) > 0$ ).

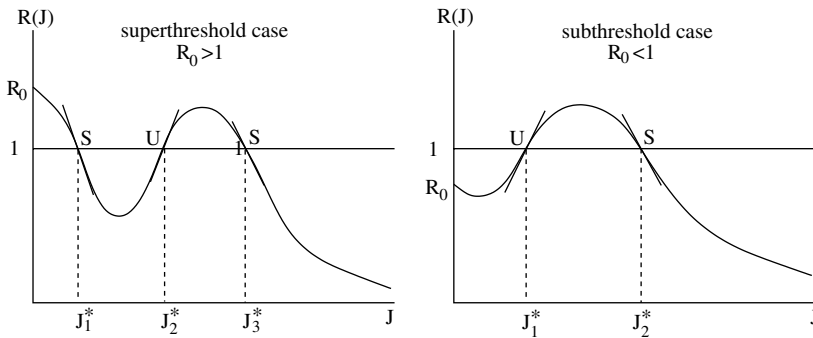


Fig. 4. The graph of the function  $R(J)$  is given. Each intersection of this graph with the horizontal line  $y = 1$  gives one nontrivial equilibrium. The slope of the tangent at the intersection point is directly related to the stability of the corresponding equilibrium. In the superthreshold case  $\mathcal{R}_0 > 1$  we have  $R'(J_1^*) < 0$ ,  $R'(J_2^*) > 0$  and  $R'(J_3^*) < 0$ . The equilibrium corresponding to  $J_2^*$  is unstable. The remaining are expected to be locally asymptotically stable, at least for most parameter values. In the subthreshold case  $R'(J_1^*) > 0$  and therefore the corresponding equilibrium is unstable. In this case we also have  $R'(J_2^*) < 0$  and the corresponding equilibrium is expected to be locally asymptotically stable.

**Proof.** This proof is technical and it is omitted. □

The proposition below gives the instability of equilibria for which  $\mu\eta'(J^*) > 1$ .

**Proposition 4.3.** *Assume the system (2.2) has equilibria which are all simple and ordered in increasing order of  $J$ . If  $\mathcal{R}_0 < 1$  and the system (2.2) has nontrivial equilibria every other one is unstable with the first one being unstable. If  $\mathcal{R}_0 > 1$  then every other nontrivial equilibrium is unstable with the second one being unstable.*

**Proof.** First we observe that if  $\lambda$  is a real variable, then  $\mathcal{Q}(\lambda; J^*) \rightarrow 0$  as  $\lambda \rightarrow \infty$  independently of the value of  $J^*$ . This property is similar to the behavior of  $\mathcal{G}(\lambda)$  (see Fig. 3) in the case of the disease-free equilibrium. Suppose that  $\mathcal{R}_0 < 1$ . Then if there are nontrivial equilibria Proposition 3.3 implies that at every odd numbered equilibrium we have  $\mu\eta'(J^*) > 1$  ( $R'(J^*) > 0$ ). Consequently, Proposition 4.2 implies that  $\mathcal{Q}(0, J^*) > 1$ .

Now suppose that  $\mathcal{R}_0 > 1$ . Then Proposition 3.3 implies that at every even numbered equilibrium we have  $\mu\eta'(J^*) > 1$  ( $R'(J^*) > 0$ ). Consequently, Proposition 4.2 implies again that  $\mathcal{Q}(0, J^*) > 1$ .

Thus, in both cases we have  $\mathcal{Q}(0, J^*) > 1$ . Hence, the equation  $\mathcal{Q}(\lambda, J^*) = 1$  has a real positive solution and the corresponding equilibrium is unstable. This completes the proof. □

For the remaining equilibria we have  $\mathcal{Q}(0, J^*) < 1$ . However, unlike the case of the disease-free equilibrium this does not guarantee us that  $|\mathcal{Q}(\lambda, J^*)| < 1$  for all  $\lambda$ . In fact, that may not be true even for real  $\lambda$  only (see Fig. 5). Consequently, if for some parameter values it happens that  $|\mathcal{Q}(\lambda, J^*)| < 1$  for all  $\lambda$  with  $\Re \lambda \geq 0$ , then the corresponding equilibrium is locally asymptotically stable. But for other parameter values it may be possible that equilibrium loses stability, perhaps through Hopf bifurcation.

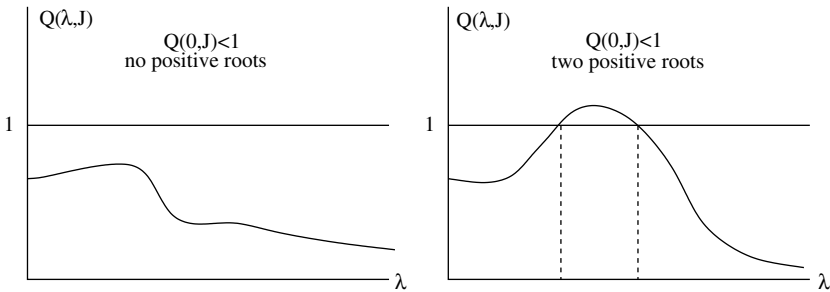


Fig. 5. The graph of the function  $\mathcal{Q}(\lambda, J^*)$  is given with  $\lambda$  being a real variable for some  $J^*$ . Both figures show the case when  $\mathcal{Q}(0, J^*) = \mathcal{R}_0 < 1$ . In the left figure there are no nonnegative real roots to the equation  $\mathcal{Q}(\lambda, J^*) = 1$ . The figure on the right shows the case when there are real positive roots of the equation  $\mathcal{Q}(\lambda, J^*) = 1$ . We have not ruled out any of these cases.

As we show in the next section, in some cases the stability criteria for endemic equilibria given by Proposition 4.3 are exact in the sense that stable and unstable endemic equilibria alternate as the value of  $J$  increases.

### 5. Dynamics of the Unstructured Model

In this section, we analyze the behavior of solutions in the unstructured case, i.e. when the functions  $\rho$ ,  $h$ , and  $\gamma$  are constant. The function  $g$  need not be constant. Integrating over  $x \in [0, +\infty)$  in the last two equations of (2.3), we find that the proportions of susceptible, infected and recovered individuals satisfy the following system

$$\begin{aligned} s'(t) &= \mu - \beta h j(t)s(t) - \mu s(t), \\ j'(t) &= \beta h j(t)s(t) + \rho h j(t)r(t) - (\gamma + \mu)j(t), \\ r'(t) &= -\rho h j(t)r(t) + \gamma j(t) - \mu r(t), \end{aligned} \tag{5.1}$$

where  $s(t) + j(t) + r(t) = 1$ . Hence, we can remove the variable  $r$  via the substitution  $r = 1 - s - j$  and analyze the reduced limiting system

$$\begin{aligned} s'(t) &= \mu - bj(t)s(t) - \mu s(t), \\ j'(t) &= j(t)(bs(t) + \tilde{b}(1 - j(t) - s(t)) - \gamma - \mu), \end{aligned} \tag{5.2}$$

where  $b = \beta h$  and  $\tilde{b} = \rho h$ . The global dynamics of (5.2) in the invariant region  $\{j > 0\}$  is very simple due to the Bendixson criterion. Indeed, choosing  $w = 1/j$ , we immediately find that

$$\frac{\partial}{\partial s}(ws') + \frac{\partial}{\partial j}(wj') = -\frac{\mu}{j} - b - \tilde{b} < 0,$$

hence (5.2) admits no periodic solutions; specifically, all positive solutions converge to an equilibrium.

At any endemic equilibrium, we have  $s = \frac{\mu}{bj + \mu}$  and if we denote by

$$\Phi(j) = (b - \tilde{b})\frac{\mu}{bj + \mu} + \tilde{b}(1 - j) \tag{5.3}$$

endemic equilibria  $\hat{j}$  satisfy the equation  $\Phi(\hat{j}) = \gamma + \mu$ . Observe that  $\Phi(0) = b$  and the differences  $\Phi(0) - (\gamma + \mu)$  and  $\mathcal{R}_0 - 1$  have identical signs. In addition,  $\Phi(1) < \mu < \gamma + \mu$ . Since equation  $\Phi(j) = \gamma + \mu$  is at most quadratic in  $j$ , there exist no more than two roots  $0 < j_1 < j_2 < 1$ . Therefore, in case of a single root  $j = j_2$ , we have that  $\Phi'(j_2) < 0$ , and in case of two roots we have that  $\Phi'(j_1) > 0 > \Phi'(j_2)$ . The variational matrix of (5.2) at an endemic equilibrium is given by

$$A = \begin{pmatrix} -\mu - bj & -bs \\ (b - \tilde{b})j & -\tilde{b}j \end{pmatrix}. \tag{5.4}$$

The trace of  $A$  is always negative and the determinant can be expressed as

$$\det A = -j(\mu + bj) \left( -\tilde{b} - (b - \tilde{b})\frac{b\mu}{(\mu + bj)^2} \right) = -j(\mu + bj)\Phi'(j).$$

We conclude that the endemic equilibrium corresponding to the smaller root  $j = j_1$  is unstable (a saddle), while the endemic equilibrium corresponding to the greater root  $j = j_2$  is asymptotically stable. Finally, existence of two endemic equilibria implies that  $\Phi(0) < \gamma + \mu$  and  $\mathcal{R}_0 < 1$ . In this case, both the disease-free equilibrium  $(1, 0)$  and the endemic equilibrium  $(1 - j_2, j_2)$  are asymptotically stable, and the systems (5.1) and (5.2) are bistable.

## 6. Concluding Remarks

Linking immunology with epidemiology in mathematical models is relatively recent. Most of the models in the literature are geared towards macroparasitic infections. Despite their simplicity, some of these models have been found to exhibit complex dynamical behavior.<sup>38</sup> More recently, a general theoretic immunoepidemiological model of microparasitic infection has been built as an attempt to link the parameters values of a simple immunological model with a classical SIR epidemiological model.<sup>14</sup> The approach in Gilchrist and Sasaki<sup>14</sup> allows for a unique infection and does not trace the acquired immunity of individuals after their recovery. It also does not allow for repeated infections with the same pathogen.

In this article, we introduce a physiological model that structures the individuals by their immune status. The main assumption of our model is that the immune status increases during the infection and remains constant after the individual recovers. This approach allows to track the immune status of the host during the infection as well as after recovery. Therefore, we are able to account for a more vigorous response of the immune system that was previously exposed to the pathogen. Our model is of SIR type but permits the recovered individuals to be reinfected. If we interpret the immune status as the number of pathogen-specific immune cells, then the growth curve of the immune status  $g(x)$  can be evaluated explicitly from the system of the immune response in Gilchrist and Sasaki.<sup>14</sup> In particular, combining the notation of this report with the notation used in Gilchrist and Sasaki,<sup>14</sup> we have  $x' = axP$  where  $P$  denotes the pathogenic load. The pathogenic load can be expressed in terms of the immune cell load of the host as  $P(x) = \frac{1}{a}(r \ln x - x + 1) + 1$  where the units are chosen so that the initial conditions are equal to one. Consequently, a reasonable choice for  $g(x)$  at least in the case when we consider an immune load of the susceptible individuals  $\bar{x}$  different from zero will be  $g(x) = x(r \ln x - x + 1) + ax$ . This function is positive only for some interval of immune cell load  $\bar{x} < x < x_{\max}$ . Thus, it cannot be used for  $x \rightarrow \infty$ . This contradiction may be resolved if the model (2.2) is set up in such a way that at each reinfection the ODE system for the pathogenic load and the immune status  $x$  is considered with different (appropriate for the individual being infected) initial conditions for the immune status.

We compute the epidemic reproduction number and study the equilibria. Reinfection may lead to backward bifurcation and produce multiple endemic equilibria when the reproduction number is below one.<sup>39</sup> Reinfection is the main mechanism that leads to backward bifurcation in our case too. Epidemiological mechanisms



such as reinfection and vaccination lead to backward bifurcation because they create several classes with different susceptibilities to the disease.<sup>40</sup> We establish necessary and sufficient conditions for backward bifurcation to occur and observe that there can be at most two subthreshold equilibria with alternating stability (the lower one is unstable) if the immune status of the hosts is not taken into account. The absence of the immune status structure allows for a unique endemic equilibrium when the epidemic reproduction number is above one. This endemic equilibrium is globally stable. However, the variability of the hosts' immune status can lead to multiple equilibria. We present a specific case when there are three endemic equilibria. We show that every other one is unstable with the even numbered being unstable. We surmise that the remaining equilibria are locally stable at least for some parameter values. In particular, in the case of three superthreshold endemic equilibria the ones corresponding to  $J_1$  and  $J_3$  are locally stable while the one corresponding to  $J_2$  is unstable. This implies that the differential immunity of the hosts is a potential biological mechanism that may lead to bistability of two nontrivial infectious distributions on the epidemic level.

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