The Effects of Female's Susceptibility on Coexistence of Multiple Pathogen Strains of Sexually Transmitted Diseases

by

Carlos Castillo-Chavez
and
Wenzhang Huang and Jia Li

BU-1307-M

Received October 1995

THE EFFECTS OF FEMALE'S SUSCEPTIBILITY ON COEXISTENCE OF MULTIPLE PATHOGEN STRAINS OF SEXUALLY TRANSMITTED DISEASES

by

Carlos Castillo-Chavez
Biometrics Unit
Center for Applied Mathematics
Mathematical Science Institute
Cornell University
Ithaca. NY 14853

Wenzhang Huang*, Jia Li*
Department of Mathematical Sciences
University of Alabama in Huntsville
Huntsville, AL 35899

May, 1995

* The work was completed while these authors were visiting the Biometrics Unit and the Center for Applied Mathematics. Cornell University.

ABSTRACT

We study the dynamics of sexually-transmitted pathogens in a heterosexually active population, where females are divided into two different groups based on their susceptibility to two distinct pathogenic strains. It is assumed that a host cannot be invaded simultaneously by both disease agents and that when symptoms appear—a function of the pathogen, strain, virulence, and an individual's degree suceptibility—then individuals are treated and/or recover. Heterogeneity in susceptibility to the acquisition of infection and/or in variability in the length of the infection period of the female subpopulations is incorporated. Pathogens' coexistence is highly unlikely on homogeneously mixing female and male populations with no heterogeneity among individuals of either gender. Variability in suceptibility in the female subpopulation makes coexistence possible albeit under a complex set of circumnstances that must include differences in contact/mixing rates between the groups of females and the male population as well as differences in the lengths of their average periods of infectiousness for the three groups. Coexistence seems quite difficult but not impossible if heterogeneity is limited.

1. Introduction

A central question in evolutionary biology, still demanding a satisfactory explanation, focuses on the evolutionary need/advantage of sexual versus asexual reproduction. A quick glance at the literature on the evolution of sexual reproduction reveals (not surprisingly) a tremendous amount of interest and research activity on this question amongst theoretical and field biologists (see Maynard Smith, 1978). Most theoretical studies on the importance of sexual reproduction have been carried out within the field of theoretical population genetics and with the help of mathematical models that must necessarily incorporate mating systems at the level of the gene. This article begins with the obvious—but often ignored—assumption that the evolution of sexually-transmitted diseases (STDs) among biological organisms must be closely linked to the evolution of sexual reproduction and, therefore, diseases that are transmitted through some type of sexual activity cannot be systematically studied without frameworks and models that include males *and* females.

In previous papers (Castillo-Chavez, Huang, and Li, 1993, 1994), we have analyzed S-I-S STD models with multiple competing strains in an exclusively heterosexually-active population and concluded that in a behaviorally and genetically homogeneous population coexistence is not possible except under very special and nongeneric circumstances. Our analysis under these assumptions is complete; that is, we have provided the global stability analysis of the stationary states for two-strain models. In addition, we have also provided the local stability analysis of models where a host faces any number competing strains. We have also partially analyzed a model extension to deal with STD dynamics in a two-sex population that is also stratified by the individuals' infection stages. This level of stratification does not increase the level of heterogeneity needed to rule out competitive exclusion.

Biologists have been concerned with evolutionary interactions that result from changing host and pathogen populations. Advances in evolutionary biology, behavior, and social dynamics have brought to the forefront of research the importance of a multitude of factors that influence not only disease dynamics but that also play a role on the evolution of virulence (Anderson and May 1991; Ewald, 1993, 1994; Brauer et al. 1992; Blythe et al. 1993; Hadeler and Castillo-Chavez 1994; Castillo-Chavez et al. 1993a,b, 1994; Heiderich et al. 1994; Velasco et al. 1994; Hsu-Schmitz 1993), Castillo-Chavez, Velasco, and Fridman 1994). Host-vector interactions such as those observed in the myxoma-rabbit system (Levin and Pimentel 1981; Levin 1983a, b; May and Anderson 1983, 1990) argue against pathogen evolution towards reduce virulence while providing rich systems for the study of coexistence and coevolution.

A useful view within the context of host-parasite systems is to think of susceptible hosts as patches available for colonization by infectious pathogens. Hence it is possible to pose general questions such as: What are the possible outcomes of coevolutionary races when different strains of the same pathogen compete for the same patches? When is competitive exclusion the rule? What happens if the quality or desirability of a patch changes over time? Mathematical models and field studies have begun to yield useful results and have helped us formulate new paradigms on which we can study the outcomes of coevolution (see Anderson and May, 1982, 1991; Beck, 1984; Bremermann and Pickering, 1983; Bremermann and Thieme, 1989; Castillo-Chavez et al., 1988, 1989; Dietz, 1979; Dwyer et al., 1990; Fenner and Myers, 1978; Fenner and Ratcliffe, 1965; Levin, 1983a, 1983b; Levin and Pimentel, 1981; May and Anderson, 1983).

This paper focusses on the dynamics of sexually-transmitted pathogens in a heterosexually active population, where females are divided into two groups based on their susceptibility to infection (colonization) by two distinct pathogenic strains of an STD.

It is assumed that a host cannot be invaded simultaneously by both disease agents (that is, there is no superinfection) and that when symptoms appear–a function of the pathogen, strain, virulence, and an individual's degree suceptibility–then individuals are treated and/or recover. Heterogeneity in susceptibility to the acquisition of infection and/or in variability in the length of the infection period of female populations is incorporated in an expanded two-sex model. The presence of only a homogeneous female group and a homogeneous male group make disease coexistence impossible. Variability in suceptibility in female subpopulations (two groups0 makes coexistence possible albeit under a complex sets of circumnstances that must take into account differences in contact/mixing rates between females and males as well as differences in the lengths of their average periods of infectiousness. Coexistence seems difficult to achieve but it is not impossible.

This manuscript is organized as follows: Section 2 introduces our model and simplifies it using some recent results on asymptotically autonomous epidemic models (Castillo-Chavez and Thieme, 1993; Thieme, 1992, 1993, 1994). The necessary thresholds are computed and the stability of the infection-free state is studied in Section 3; A principle of competitive exclusion for SIS models with homogeneous mixing is established in Section 4; Section 5 provides our coexistence results; and in Section 6 we discuss the consequences of our results and outline some future work.

2. Model Description And The Generated Monotone Flow

The use of differential equations for STD models began with Ross in 1911. Ross introduced a differential equation model for the transmission dynamics of vector-transmitted diseases which, as he recognized, was formally equivalent to a model for the transmission dynamics of STDs. Ross' theoretical work was driven by his efforts to develop

management strategies for the control of malaria. The formulation of the first explicit STD model, a gonorrhea model, is due to Cooke and Yorke (1973).

An important observation made by Ross is that the average total rate of contacts between host and vectors must be conserved (Ross, 1911, p.667). This simple conservation law of contact rates has become the basis for modeling heterogeneous contact structures (Busenberg and Castillo-Chavez, 1989, 1991; Castillo-Chavez and Busenberg, 1991). We use it in this Section.

A common but limiting assumption is that the sizes of the interacting sexually-active populations are constant (Lajmanovich and Yorke, 1976; Hethcote and Yorke, 1984; and references therein). Variable population size may seriously impact the qualitative dynamics of epidemic models (Castillo-Chavez et al., 1989a; Huang et al., 1992). Here it is assumed that the population under consideration does not experience disease induced mortality. We also assume assume that the recruitment of new hosts (all suceptible) occurs at a constant rate and, consequently, the total population sizes of males and females (both groups) become asymptotically constant. It is therefore possible to replace the "real" model with a an asymptotically autonomous limiting system (see Thieme, 1992; Thieme 1993, 1993a; Castillo-Chavez and Thieme, 1994). Consequently, we implicitly assume (as Lajmanovich and Yorke, 1976) that social dynamics does not play any role on the qualitative dynamics of the model. This is a strong assumption/limitation which is justified, in part, because our efforts are directed to the study of the dynamics of two competing strains in a *minimally* heterogeneous population.

To be explicit, we consider an S-I-S STD model for a heterosexually-active population. The population consists of susceptibles and infecteds. Among the population, there are two different groups of female individuals in the transmission of diseases, denoted by superscripts f and c, which are determined by their sexual behavior, ge-

netics, or other factors. We assume that the infecteds are divided into 2 classes based on the pathogen strains in their body, and that susceptibles infected by infecteds with a certain pathogen strain have the same pathogen strain. We use S^k, $k = m, f, c$ to denote the susceptible males, susceptible females in two different groups, and use I_i^k, $k = m, f, c$, $i = 1, 2$, to denote the infecteds with strain i. Then the dynamics of the spread of the disease are governed by

$$\begin{cases} \dot{S}^m = \Lambda^m - B^m - \mu S^m + \sum_i \gamma_i^m I_i^m, \\ \dot{I}_i^m = B_i^m - (\mu + \gamma_i^m) I_i^m, \\ \dot{S}^f = \Lambda^f - B^f - \mu S^f + \sum_i \gamma_i^f I_i^f, \\ \dot{I}_i^f = B_i^f - \left(\mu + \gamma_i^f\right) I_i^f, \\ \dot{S}^c = \Lambda^c - B^c - \mu^c S^c + \sum_i \gamma_i^c I_i^c, \\ \dot{I}_i^c = B_i^c - (\mu^c + \gamma_i^c) I_i^c, \end{cases} \tag{2.1}$$

where

$$\begin{aligned} B_i^m &= r^m \left(T^m, T^f, T^c\right) S^m \left(\beta_i^f \frac{I_i^f}{T^f} + \beta_i^c \frac{I_i^c}{T^c}\right), \\ B_i^f &= r^f \left(T^m, T^f, T^c\right) S^f \beta_i^m \frac{I_i^m}{T^m}, \\ B_i^c &= r^c \left(T^m, T^f, T^c\right) S^c \beta_i^m \frac{I_i^m}{T^m}, \\ B^m &= \sum_{i=1}^{2} B_i^m, \quad B^f = \sum_{i=1}^{2} B_i^f, \quad B^c = \sum_{i=1}^{2} B_i^c, \end{aligned}$$

with the constraint

$$r^m \left(T^m, T^f, T^c\right) T^m = r^f \left(T^m, T^f, T^c\right) T^f + r^c \left(T^m, T^f, T^c\right) T^c. \tag{2.2}$$

Here Λ^k, $k = m, f, c$ denote the input flow (recruitment) entering the sexually active subpopulations; $1/\mu^c$ is the average sexual life span for people in group c, and $1/\mu$ is

the average sexual life span for people not in group c; γ_i^k are the rates of recovery; $T^k = S^k + \sum_j I_j^k$ are the total number of males, females in group f and group c, respectively; r^k, as functions of T^m, T^f, and T^c, are the numbers of partners per individual per unit of time; and β_i^k are the rates of infection. The constraint indicates that the total number of female sexual partners of males per unit of time and the total number of male partners of females per unit of time given the current availability of partners must be balanced.

Since $T^k = S^k + \sum_i^N I_i^k$, (2.1) is equivalent to

$$\begin{cases} \dot{T}^m = \Lambda^m - \mu T^m, \\ \dot{T}^f = \Lambda^f - \mu T^f, \\ \dot{T}^c = \Lambda^c - \mu^c T^c, \\ \dot{I}_i^m = -\left(\mu + \gamma_i^m\right) I_i^m + r^m\left(T^m, T^f, T^c\right)\left(T^m - \sum_j I_j^m\right)\left(\beta_j^f \frac{I_j^f}{T^f} + \beta_j^c \frac{I_i^c}{T^c}\right), \\ \dot{I}_i^f = -\left(\mu + \gamma_i^f\right) I_i^f + r^f\left(T^m, T^f, T^c\right) \beta_i^m \frac{\left(T^f - \sum_j I_j^f\right) I_i^m}{T^m}, \\ \dot{I}_i^c = -\left(\mu^c + \gamma_i^c\right) I_i^c + r^c\left(T^m, T^f, T^c\right) \beta_i^m \frac{\left(T^c - \sum_j I_j^c\right) I_i^m}{T^m}. \end{cases} \tag{2.3}$$

The asymptotic equilibrium values for T^k are

$$T^m = \frac{\Lambda^m}{\mu}, \qquad T^f = \frac{\Lambda^f}{\mu}, \qquad T^c = \frac{\Lambda^c}{\mu^c}.$$

If we define

$$b^m := r^m\left(\Lambda^m/\mu^m, \Lambda^f/\mu^f, \Lambda^c/\mu^c\right), b^f := r^f\left(\Lambda^m/\mu^m, \Lambda^f/\mu^f, \Lambda^c/\mu^c\right), b^c := r^c\left(\Lambda^m/\mu^m, \Lambda^f/\mu^f,\right.$$

Then it follows from the constraint (2.2) that

$$\mu^c\left(b^m\Lambda^m - b^f\Lambda^f\right) = \mu b^c \Lambda^c,$$

as $t \to \infty$.

The limiting system of (2.1) or (2.3) is therefore given by the following set of equations:

$$\begin{aligned}
\dot{I}_i^m &= -\left(\mu+\gamma_i^m\right) I_i^m + b^m \left(\frac{\Lambda^m}{\mu} - \sum_j I_j^m\right)\left(\beta_i^f \frac{\mu}{\Lambda^f} I_i^f + \beta_i^c \frac{\mu^c}{\Lambda^c} I_i^c\right), \\
\dot{I}_i^f &= -\left(\mu+\gamma_i^f\right) I_i^f + \frac{\mu b^f \beta_i^m}{\Lambda^m}\left(\frac{\Lambda^f}{\mu} - \sum_j I_j^f\right) I_i^m, \qquad (2.4) \\
\dot{I}_i^c &= -\left(\mu^c+\gamma_i^c\right) I_i^c + \frac{\mu b^c \beta_i^m}{\Lambda^m}\left(\frac{\Lambda^c}{\mu^c} - \sum_j I_j^c\right) I_i^m.
\end{aligned}$$

To simplify the notation, we define the following quantities:

$\sigma_i^k := \left(\mu+\gamma_i^k\right)$, $k = m, f$, $\sigma_i^c := \left(\mu^c+\gamma_i^c\right)$, $p^k := \dfrac{\Lambda^k}{\mu}$, $k = m, f$, $p^c := \dfrac{\Lambda^c}{\mu^c}$, $a_i^m := \dfrac{b^m \beta_i^f}{p^f}$, $a_i^f := \dfrac{b^f \beta_i^m}{p^m}$, $a_i^c := \dfrac{b^c \beta_i^m}{p^m}$, and $a_i^{mc} := \dfrac{b^m \beta_i^c}{p^c}$.

System (2.4) can therefore be rewritten as

$$\begin{aligned}
\dot{I}_i^m &= -\sigma_i^m I_i^m + \left(p^m - \sum_j I_j^m\right)\left(a_i^m I_i^f + a_i^{mc} I_i^c\right), \\
\dot{I}_i^f &= -\sigma_i^f I_i^f + a_i^f \left(p^f - \sum_j I_j^f\right) I_i^m, \qquad (2.5) \\
\dot{I}_i^c &= -\sigma_i^c I_i^c + a_i^c \left(p^c - \sum_j I_j^c\right) I_i^m.
\end{aligned}$$

If we now let

$$\mathbb{R}_+^6 := \left\{\left(I_1^m, I_1^f, I_1^c, I_2^m, I_2^f, I_2^c\right); \quad I_i^k \geq 0,\ k = m, f, c, \quad i = 1, 2\right\},$$

and define the subset of $\mathbb{R}_+^6$ by

$$\Omega := \left\{\left(I_1^m, I_1^f, I_1^c, I_2^m, I_2^f, I_2^c\right) \in \mathbb{R}_+^6; \quad \sum_{j=1}^2 I_j^m \leq p^m, \quad \sum_{j=1}^2 I_j^f \leq p^f, \quad \sum_{j=1}^2 I_j^c \leq p^c\right\},$$

we then observe that the flow generated by (2.5) is positively invariant on Ω. Furthermore, the flow is monotone under the special order (see Castillo-Chavez et al. 1994) given by

Definition 2.1. *Let* $K = \{x = (x_1, \cdots, x_6) \in \mathbb{R}^6; x_i \geq 0, i = 1,2,3,\ x_j \leq 0, j = 4,5,6\}$. *A type* K *order, denoted by* " $\leq_K$ ", *is defined in such a way that*

$$x \leq_K y \qquad \text{if and only if} \quad x - y \in K. \tag{2.6}$$

Using this order, it is easily seen that the flow generated by (2.5) is monotone.

Theorem 2.2. *Let* $I = \left(I_1^m, I_1^f, I_1^c, I_2^m, I_2^f, I_2^c\right)$ *and let* $I(t, I_0)$ *be a solution of (2.5) with* $I(0, I_0) = I_0$. *Then*

$$I\left(t, I_0^a\right) \leq_K I\left(t, I_0^b\right), \quad t \geq 0,$$

if $I_0^a, I_0^b \in \Omega$ *and* $I_0^a \leq_K I_0^b$.

Proof. Let $Q = \text{diag}(q_i)$ with $q_1 = q_2 = q_3 = 1$, $q_4 = q_5 = q_6 = -1$. Then the matrix $QJ(I)Q$ has nonnegative off-diagonal elements for every $I \in \Omega$, where $J(I)$ is the Jacobian matrix of (2.5) evaluated at I. It follows from Lemma 2.1 in Smith (1988) that the flow $I(t, I_0)$ preserves a type K order on Ω; that is, the flow is monotone under this type K order.

3. Thresholds

The linearization about the infection-free equilibrium of System (2.5) is

$$\begin{pmatrix} \dot{I}_i^m \\ \dot{I}_i^f \\ \dot{I}_i^c \end{pmatrix} = \begin{pmatrix} -\sigma_i^m & p^m a_i^m & a_i^{mc} \\ p^f a_i^f & -\sigma_i^f & 0 \\ p^c a_i^c & 0 & -\sigma_i^c \end{pmatrix} \begin{pmatrix} I_i^m \\ I_i^f \\ I_i^c \end{pmatrix}, \qquad i = 1,2. \tag{3.1}$$

System (3.1) consists of two decoupled systems of three equations. The diagonal elements of the coefficient matrix of each system are negative and the off-diagonal elements are nonnegative. Then, from the theory of M-matrices, it is easy to see that if

$$p^m p^f a_i^m a_i^f \sigma_i^c + p^m p^c a_i^{mc} a_i^c \sigma_i^f < \sigma_i^m \sigma_i^f \sigma_i^c, \qquad \forall i,$$

then the infection-free equilibrium is table, and that if there exists $i = 1$, or 2, such that

$$p^m p^f a_i^m a_i^f \sigma_i^c + p^m p^c a_i^{mc} a_i^c \sigma_i^f > \sigma_i^m \sigma_i^f \sigma_i^c,$$

the infection-free equilibrium is unstable. Define the reproductive number, R_i, in the ith subgroup by

$$\begin{aligned} R_i :=& \frac{p^m p^f a_i^m a_i^f \sigma_i^c + p^m p^c a_i^{mc} a_i^c \sigma_i^f}{\sigma_i^m \sigma_i^f \sigma_i^c} \\ =& b^m \beta_i^m \frac{\left(\mu^c + \gamma_i^c\right) b^f \beta_i^f + \left(\mu + \gamma_i^f\right) b^c \beta_i^c}{\left(\mu + \gamma_i^m\right)\left(\mu + \gamma_i^f\right)\left(\mu^c + \gamma_i^c\right)}. \end{aligned} \tag{3.2}$$

We can now make the following observations: If $R_i \leq 1$, $\left(I_i^m, I_i^f, I_i^c\right) \to (0,0,0)$. If $R_i \leq 1$ for both $i = 1$ and 2 then the infection-free equilibrium is stable; that is, $R_i \leq 1$ for both $i = 1$ and 2 leads to the extinction of the disease in the population. If there exists at least one strain such that $R_i > 1$ then $\left(I_i^m, I_i^f, I_i^c\right) \not\to (0,0,0)$, that is, the disease will spread in the population.

R^k will characterize the reproduction numbers of the three different groups respectively.

Hence

$$R_i^m := \frac{b^m \beta_i^m}{\mu + \gamma_i^m}, \quad R_i^f := \frac{b^f \beta_i^f}{\mu + \gamma_i^f}, \quad R_i^c := \frac{b^c \beta_i^c}{\mu^c + \gamma_i^c}, \tag{3.3}$$

and consequently

$$R_i = R_i^m \left(R_i^f + R_i^c\right).$$

Following the approach in Castillo-Chavez et al. (1994), it can be shown that the infection-free equilibrium and the boundary equilibrium (given explicitly in the next section) of this model are globally stable under the appropriate threshold conditions. Here we only state the results, that is, we omit the details as the approach follows directly from our published work (see Castillo-Chavez et al. 1994).

Lemma 3.1. *Let* $E_1 = \left(I_1^m, I_1^f, I_1^c, 0, 0, 0\right)$ *and* $E_2 = \left(0, 0, 0, I_2^m, I_2^f, I_2^c\right)$ *be equilibria of (2.5), where* $I_i^m, I_i^f, I_i^c > 0$, *if* $R_i > 1$, *and* $I_i^m = I_i^f = I_i^c = 0$, *if* $R_i \leq 1$. *Let* $\xi^1 = \left(p^m, p^f, p^c, 0, 0, 0\right)$ *and* $\xi^2 = \left(0, 0, 0, p^m, p^f, p^c\right)$. *Then*

$$\lim_{t \to \infty} I\left(t, \xi^i\right) = E_i, \qquad i = 1, 2.$$

Theorem 3.2. *Let the reproductive number* R_i *for each group be defined in (3.2). If* $R_i \leq 1$ *for both* $i = 1, 2$ *then the epidemic goes extinct regardless of the initial levels of infection . If on the other hand* $R_i > 1$ *for* $i = 1$ *or* $i = 2$ *then the epidemic will spread in the population.*

4. Competitive Exclusion

Because the model that we are investigating in this paper is decomposable then there exist two types of endemic equilibria: one type consisting of *only* one nonzero triple $\left(I_i^m, I_i^f, I_i^c\right)$ and a second type will all positive components. We call the first type boundary equilibria and the second type coexistence equilibria.

4.1. Existence of the Boundary Equilibrium.

The boundary equilibrium always exists whenever the epidemic spreads in the population. We collect this result in the following theorem:

Theorem 4.1.1. *Assume that* $R_i > 1$, $i = 1, 2$. *Then the nontrivial equilibrium* $\left(S^k > 0, I_i^k > 0, I_j^k = 0, j \neq i\right)$ *exists.*

Proof. We need to solve

$$\sigma_i^m I_i^m = (p^m - I_i^m)\left(a_i^m I_i^f + a_i^{mc} I_i^c\right), \tag{4.1.1a}$$

$$\sigma_i^f I_i^f = a_i^f \left(p^f - I_i^f\right) I_i^m, \tag{4.1.1b}$$

$$\sigma_i^c I_i^c = a_i^c \left(p^c - I_i^c\right) I_i^m, \tag{4.1.1c}$$

for I_i^k, $0 < I_i^k < p^k$.

First, we solve (4.1.1b) and (4.1.1c) to get

$$I_i^f = \frac{p^f a_i^f I_i^m}{\sigma_i^f + a_i^f I_i^m}, \qquad I_i^c = \frac{p^c a_i^c I_i^m}{\sigma_i^c + a_i^c I_i^m}. \tag{4.1.2}$$

Substituting (4.1.2) into (4.1.1a) yields

$$\frac{\sigma_i^m}{p^m - I_i^m} - \left(\frac{p^f a_i^m a_i^f}{\sigma_i^f + a_i^f I_i^m} + \frac{p^c a_i^{mc} a_i^c}{\sigma_i^c + a_i^c I_i^m}\right) = 0. \tag{4.1.3}$$

The left hand side of (4.1.3) can be seen as a function of $_i^m$, namely $f\left(I_i^m\right)$. It is easy to check that $f'(I_i^m) > 0$ and that $\lim_{I_i^m \to p^m} f(I_i^m) = +\infty$. Consequently, (4.1.3) has a unique solution $0 < I_i^m < p^m$ if and only if $f(0) < 0$. Furthermore, because

$$f(0) = \frac{\sigma_i^m}{p^m} - \left(\frac{p^f a_i^m a_i^f}{\sigma_i^f} + \frac{p^c a_i^{mc} a_i^c}{\sigma_i^c}\right) = \frac{\sigma_i^m}{p^m}\left(1 - R_i\right),$$

then it follows that there exists a unique positive solution I_i^m of (4.1.3) if and only if $R_i > 1$. This unique positive I_i^m uniquely determines positive I_i^f and I_i^c via Equation (4.1.2). The proof then is complete.

Remark. The component I_i^m of the nontrivial equilibrium, or the solution of (4.1.3), can be represented by the following explicit formula

$$I_i^m = \frac{\sqrt{K_2^2 - 4K_1K_3} - K_2}{2K_1},$$

where

$$
\begin{aligned}
K_1 =& a_i^f a_i^c \left(\sigma_i^m + b_i^m \left(\beta_i^f + \beta_i^c\right)\right), \\
K_2 =& \sigma_i^m \left(a_i^c \sigma_i^f + a_i^f \sigma_i^c\right) + p^f a_i^m a_i^f \sigma_i^c + p^c a_i^{mc} a_i^c \sigma_i^f - p^m \left(p^f a_i^m a_i^f a_i^c + p^c a_i^{mc} a_i^f a_i^c\right) \\
=& \frac{\sigma_i^m \sigma_i^f \sigma_i^c}{p^m} \left(\frac{\beta_i^m}{\beta_i^c}\left(R_i^c - R_i\right) + \frac{\beta_i^m}{\beta_i^f}\left(R_i^f - R_i\right) + R_i\right), \\
K_3 =& \sigma_i^m \sigma_i^f \sigma_i^c \left(1 - R_i\right).
\end{aligned}
$$

Because $K_3 < 0$ and because there is only one positive solution of (4.1.3) then it follows since I_i^m is the solution of a quadratic equation that K_2 must be positive.

4.2 Stability of the Boundary Equilibrium.

The Jacobian at the equilibrium $\left(I_1^k = 0, I_2^k > 0, k = m, f, c\right)$ has the form

$$
J = \begin{pmatrix} A_{11} & 0 \\ A_{21} & A_{22} \end{pmatrix},
$$

where

$$
A_{ii} := \begin{pmatrix} -\sigma_i^m - \delta_{2i}\left(a_2^m I_2^f + a_2^{mc} I_2^c\right) & a_i^m \left(p^m - I_2^m\right) & a_i^{mc}\left(p^m - I_2^m\right) \\ a_i^f \left(p^f - I_2^f\right) & -\sigma_i^f - \delta_{2i} a_2^f I_2^m & 0 \\ a_i^c \left(p^c - I_2^c\right) & 0 & -\sigma_i^c - \delta_{2i} a_2^c I_2^m \end{pmatrix}, \qquad i = 1, 2,
$$

$$
A_{21} = \begin{pmatrix} -\left(a_2^m I_2^f + a_2^{mc} I_2^c\right) & 0 & 0 \\ 0 & -a_2^f I_2^m & 0 \\ 0 & 0 & -a_2^c I_2^m \end{pmatrix}, \tag{4.2.1}
$$

with δ_{ij} being the Kronecker delta function.

In order to show that the matrix A_{22} is always locally stable, we need to establish the following lemma:

Lemma 4.2.1. *Let A be an $n \times n$ irreducible matrix with all off-diagonal elements nonnegative and $B = \mathrm{diag}(b_j)$ with $b_j < 0$, $j = 1, \cdots, n$. If all nonzero eigenvalues of A have negative real parts, then all eigenvalues of $A + B$ have negative real parts.*

Proof. First, from the well-known M-matrices theory, there exists a positive vector x such that $Ax \leq 0$ and therefore $(A+B)x = Ax + (b_1x_1, \ldots, b_nx_n) < 0$. Hence, it follows that all eigenvalues of $A+B$ have negative real parts (Fiedler and Pták, 1962; Poole and Boullion, 1974).

Now, because

$$A_{22} = \begin{pmatrix} -\sigma_2^m - \left(a_2^m I_2^f + a_2^{mc} I_2^c\right) & a_2^m \left(p^m - I_2^m\right) & a_2^{mc}\left(p^m - I_2^m\right) \\ a_2^f \left(p^f - I_2^f\right) & -\sigma_2^f - a_2^f I_2^m & 0 \\ a_2^c \left(p^c - I_2^c\right) & 0 & -\sigma_2^c - a_2^c I_2^m \end{pmatrix}$$

then we only need to show that all nonzero eigenvalues of the matrix

$$\widehat{J} := \begin{pmatrix} -\sigma_2^m & a_2^m \left(p^m - I_2^m\right) & a_2^{mc}\left(p^m - I_2^m\right) \\ a_2^f \left(p^f - I_2^f\right) & -\sigma_2^f & 0 \\ a_2^c \left(p^c - I_2^c\right) & 0 & -\sigma_2^c \end{pmatrix}$$

have negative real parts. Then it follows from Lemma 4.2.1 that A_{22} is stable.

It is easy to check that $\det \widehat{J} = 0$ and $\mathrm{tr}\widehat{J} = -\sum_{k=m,f,c} \sigma_2^k < 0$. Let $\widehat{J}_{ij}$ be the 2×2 principal minor with row i and column j of $\widehat{J}$. Then

$$\begin{aligned} \widehat{J}_{12} =& \frac{\sigma_2^m \sigma_2^f a_2^{mc} I_2^c}{a_2^m I_2^f + a_2^{mc} I_2^c} > 0, \\ \widehat{J}_{13} =& \frac{\sigma_2^m \sigma_2^c a_2^m I_2^f}{a_2^m I_2^f + a_2^{mc} I_2^c} > 0, \\ \widehat{J}_{23} =& \sigma_2^f \sigma_2^c > 0. \end{aligned}$$

Hence, $\widehat{J}$ has a zero eigenvalue and two eigenvalues with negative real parts, which implies that A_{22} is locally stable. The stability of the nontrivial equilibrium $\left(I_1^k = 0, I_2^k > 0, k = m,\right.$ is determined from the stability of the matrix A_{11}.

We note thatA_{11} is unstable if

$$\begin{aligned} \det A_{11} =& \sigma_1^f a_1^c a_1^{mc} \left(p^m - I_2^m\right)\left(p^c - I_2^c\right) - \sigma_1^c \left(\sigma_1^m \sigma_1^f - a_1^m a_1^f \left(p^m - I_2^m\right)\left(p^f - I_2^f\right)\right) \\ =& \frac{\sigma_1^f a_1^c a_1^{mc} \sigma_2^m \sigma_2^c I_2^c}{a_2^c \left(a_2^m I_2^f + a_2^{mc} I_2^c\right)} + \frac{\sigma_1^c a_1^m a_1^f \sigma_2^m \sigma_2^f I_2^f}{a_2^f \left(a_2^m I_2^f + a_2^{mc} I_2^c\right)} - \sigma_1^m \sigma_1^f \sigma_1^c > 0. \end{aligned}$$

Let

$$W_1 := a_1^m a_1^f \sigma_2^m \sigma_2^f - a_2^m a_2^f \sigma_1^m \sigma_1^f, \qquad W_2 := a_1^{mc} a_1^c \sigma_2^m \sigma_2^c - a_2^{mc} a_2^c \sigma_1^m \sigma_1^c.$$

Then $\det A_{11}$ can be rewritten as

$$\begin{aligned}\det A_{11} =& \frac{\sigma_1^c a_2^c \left(a_1^m a_1^f \sigma_2^m \sigma_2^f - a_2^m a_2^f \sigma_1^m \sigma_1^f\right) I_2^f + \sigma_1^f a_2^f \left(a_1^{mc} a_1^c \sigma_2^m \sigma_2^c - a_2^{mc} a_2^c \sigma_1^m \sigma_1^c\right) I_2^c}{a_2^c a_2^f \left(a_2^m I_2^f + a_2^{mc} I_2^c\right)} \\ =& \frac{\sigma_1^c \sigma_1^f}{a_2^m I_2^f + a_2^{mc} I_2^c} \left(\frac{I_2^f}{\sigma_1^f a_2^f} W_1 + \frac{I_2^c}{\sigma_1^c a_2^c} W_2\right) \\ =& \frac{\sigma_1^c \sigma_1^f I_2^m}{a_2^m I_2^f + a_2^{mc} I_2^c} \left(\frac{p^f}{\sigma_1^f \left(\sigma_2^f + a_2^f I_2^m\right)} W_1 + \frac{p^c}{\sigma_1^c \left(\sigma_2^c + a_2^c I_2^m\right)} W_2\right).\end{aligned}$$

A straightforward algebraic manipulation yields

$$\begin{aligned}\det A_{11} =& \frac{\sigma_1^m \sigma_1^f \sigma_1^c \sigma_2^m I_2^m}{\left(a_2^m I_2^f + a_2^{mc} I_2^c\right)\left(\sigma_2^f + a_2^f I_2^m\right)\left(\sigma_2^c + a_2^c I_2^m\right)} \\ & \cdot \left(p^f \sigma_2^f \left(\sigma_2^c + a_2^c I_2^m\right)\left(R_1^m R_1^f - R_2^m R_2^f\right) + p^c \sigma_2^c \left(\sigma_2^f + a_2^f I_2^m\right)\left(R_1^m R_1^c - R_2^m R_2^c\right)\right).\end{aligned}$$

If we denote

$$\left(R_1^m R_1^f - R_2^m R_2^f\right) = \Delta_1$$

and

$$\left(R_1^m R_1^c - R_2^m R_2^c\right) = \Delta_2$$

Then if $\Delta_1 > 0$ and $\Delta_2 > 0$ then the boundary equilibrium $\left(I_1^k = 0, I_2^k > 0\right)$ is unstable. On the other hand, if $\Delta_1 < 0$, $\Delta_2 < 0$, and $\det A_{11} < 0$ then since the diagonal elements of A_{11} are negative and the off-diagonal elements are nonnegative, it follows from M-matrix theory that A_{11} is stable.

In summary, we arrive at the following result:

Theorem 4.2.2. *Let $R_i^k > 1$ be defined as in (3.2). Then if*

$$R_1^m R_1^f > (<) R_2^m R_2^f \quad \text{and} \quad R_1^m R_1^c > (<) R_2^m R_2^c,$$

the boundary equilibrium $\left(I_1^k > 0, I_2^k = 0\right)$ is stable (unstable) and $\left(I_1^k = 0, I_2^k > 0\right)$ is unstable (stable).

We may think of these equilibria as the the result of competition for resources between two populations of pathogens. Hence, if $\Delta_1 \cdot \Delta_2 > 0$, one of the boundary equilibria is stable and the other is unstable, which implies one strain wins and the other loses. Hence, under the hypotheses in Theorem 4.2.2, the principle of competitive exclusion holds for the two competing strains.

5. Coexistence

5.1. Existence And Uniqueness Of The Positive Endemic Equilibrium.

In order to have coexistence, we need to solve

$$\begin{cases} \sigma_i^m I_i^m = \left(p^m - \left(I_1^m + I_2^m\right)\right)\left(a_i^m I_i^f + a_i^{mc} I_i^c\right), \\ \sigma_i^f I_i^f = a_i^f \left(p^f - \left(I_1^f + I_2^f\right)\right) I_i^m, \\ \sigma_i^c I_i^c = a_i^c \left(p^c - \left(I_1^c + I_2^c\right)\right) I_i^m, \end{cases} \tag{5.1.1}$$

for I_i^k. From $(5.1.1)_2$,

$$\begin{cases} \left(\sigma_1^f + a_1^f I_1^m\right) I_1^f + a_1^f I_1^m I_2^f = a_1^f p^f I_1^m, \\ a_2^f I_2^m I_1^f + \left(\sigma_2^f + a_2^f I_2^m\right) I_2^f = a_2^f p^f I_2^m. \end{cases} \tag{5.1.2}$$

Solving (5.1.2) yields

$$\begin{cases} I_1^f = \dfrac{p^f a_1^f \sigma_2^f I_1^m}{\sigma_1^f \sigma_2^f + a_1^f \sigma_2^f I_1^m + a_2^f \sigma_1^f I_2^m}, \\ I_2^f = \dfrac{p^f a_2^f \sigma_1^f I_2^m}{\sigma_1^f \sigma_2^f + a_1^f \sigma_2^f I_1^m + a_2^f \sigma_1^f I_2^m}. \end{cases} \tag{5.1.3}$$

Similarly,

$$\begin{cases} I_1^c = \dfrac{p^c a_1^c \sigma_2^c I_1^m}{\sigma_1^c \sigma_2^c + a_1^c \sigma_2^c I_1^m + a_2^c \sigma_1^c I_2^m}, \\ I_2^c = \dfrac{p^c a_2^c \sigma_1^c I_2^m}{\sigma_1^c \sigma_2^c + a_1^c \sigma_2^c I_1^m + a_2^c \sigma_1^c I_2^m}. \end{cases} \tag{5.1.4}$$

Set

$$A_1 := p^f a_1^m a_1^f \sigma_2^f / \sigma_1^m, \qquad A_2 := p^c a_1^{mc} a_1^c \sigma_2^c / \sigma_1^m,$$

$$D_1 := p^f a_2^m a_2^f \sigma_1^f / \sigma_2^m, \qquad D_2 := p^c a_2^{mc} a_2^c \sigma_1^c / \sigma_2^m,$$

$$B_1 := \sigma_1^f \sigma_2^f, \quad B_2 := a_1^f \sigma_2^f, \quad B_3 := a_2^f \sigma_1^f,$$
$$C_1 := \sigma_1^c \sigma_2^c, \quad C_2 := a_1^c \sigma_2^c, \quad C_3 := a_2^c \sigma_1^c.$$

Then, by substituting (5.1.3) and (5.1.4) into $(5.1.1)_1$, we have

$$\begin{cases} \dfrac{1}{p^m - \left(I_1^m + I_2^m\right)} = \dfrac{A_1}{B_1 + B_2 I_1^m + B_3 I_2^m} + \dfrac{A_2}{C_1 + C_2 I_1^m + C_3 I_2^m}, \\ \dfrac{1}{p^m - \left(I_1^m + I_2^m\right)} = \dfrac{D_1}{B_1 + B_2 I_1^m + B_3 I_2^m} + \dfrac{D_2}{C_1 + C_2 I_1^m + C_3 I_2^m}. \end{cases} \tag{5.1.5}$$

From (5.1.5), it follows that

$$\Big(C_2\big(A_1 - D_1\big) + B_2\big(A_2 - D_2\big)\Big) I_1^m =$$
$$- \Big(\big(B_1(A_2 - D_2) + C_1(A_1 - D_1)\big) + \big(B_3(A_2 - D_2) + C_3(A_1 - D_1)\big) I_2^m\Big),$$

or equivalently,

$$\beta_1^m\big(\beta_1^c R_1^c \Delta_1 + \beta_1^f R_1^f \Delta_2\big) I_1^m + \beta_2^m\big(\beta_2^c R_2^c \Delta_1 + \beta_2^f R_2^f \Delta_2\big) I_2^m = -p^m(\Delta_1 + \Delta_2). \tag{5.1.6}$$

If both $\Delta_1 > 0$ and $\Delta_2 > 0$ or if both $\Delta_1 < 0$ and $\Delta_2 < 0$ then (5.1.6) gives a line that does not go through the first quadrant and, consequently, there is no positive solution $\left(I_1^m > 0, I_2^m > 0\right)$ for (5.1.5). Hence we have the following result:

Theorem 5.1.1. *Coexistence is not possible if* $\Delta_1 \cdot \Delta_2 = \left(R_1^m R_1^f - R_2^m R_2^f\right) \cdot \left(R_1^m R_1^c - R_2^m R_2^c\right) > 0$, *that is, either* $R_1^m R_1^k > R_2^m R_2^k$, *or* $R_1^m R_1^k < R_2^m R_2^k$, *for both* $k = f, c$.

Now we consider the case of $\Delta_1 \cdot \Delta_2 < 0$, which is equivalent to

$$\frac{R_1^f}{R_2^f} > \frac{R_2^m}{R_1^m} > \frac{R_1^c}{R_2^c},$$

or

$$\frac{R_1^f}{R_2^f} < \frac{R_2^m}{R_1^m} < \frac{R_1^c}{R_2^c}.$$

Solving (5.1.6) for I_1^m gives

$$I_1^m = \alpha_1 I_2^m + \alpha_2, \tag{5.1.7}$$

where

$$\begin{aligned} \alpha_1 &:= -\frac{\beta_2^m\left(\beta_2^c R_2^c \Delta_1 + \beta_2^f R_2^f \Delta_2\right)}{\beta_1^m\left(\beta_1^c R_1^c \Delta_1 + \beta_1^f R_1^f \Delta_2\right)}, \\ \alpha_2 &:= -\frac{p^m(\Delta_1 + \Delta_2)}{\beta_1^m\left(\beta_1^c R_1^c \Delta_1 + \beta_1^f R_1^f \Delta_2\right)}. \end{aligned} \tag{5.1.8}$$

Then, substituting (5.1.7) into (5.1.5) gives the following equation

$$\begin{aligned} &\frac{1}{p^m - \alpha_2 - (\alpha_1 + 1)I_2^m} \\ &\quad - \left(\frac{A_1}{B_1 + B_2\alpha_2 + (B_2\alpha_1 + B_3)I_2^m} + \frac{A_2}{C_1 + C_2\alpha_2 + (C_2\alpha_1 + C_3)I_2^m}\right) = 0. \end{aligned} \tag{5.1.9}$$

However, since α_1 and α_2 can be rewritten as

$$\begin{aligned} \alpha_1 &= -\frac{B_1C_3\Delta_1 + B_3C_1\Delta_2}{B_1C_2\Delta_1 + B_2C_1\Delta_2}, \\ \alpha_2 &= -\frac{B_1C_1\left(\Delta_1 + \Delta_2\right)}{B_1C_2\Delta_1 + B_2C_1\Delta_2}, \end{aligned}$$

a simple calculation shows that

$$\frac{B_1 + B_2\alpha_2}{B_2\alpha_1 + B_3} = \frac{C_1 + C_2\alpha_2}{C_2\alpha_1 + C_3}.$$

Using the above results, we see that (5.1.9) is reduced to

$$\frac{1}{p^m - \alpha_2 - (\alpha_1 + 1)I_2^m} = \frac{\dfrac{A_1}{B_2\alpha_1 + B_3} + \dfrac{A_2}{C_2\alpha_1 + C_3}}{\dfrac{B_1 + B_2\alpha_2}{B_2\alpha_1 + B_3} + I_2^m},$$

or equivalently to

$$p^m - \alpha_2 - (\alpha_1 + 1)I_2^m = \frac{\dfrac{B_1 + B_2\alpha_2}{B_2\alpha_1 + B_3} + I_2^m}{\dfrac{A_1}{B_2\alpha_1 + B_3} + \dfrac{A_2}{C_2\alpha_1 + C_3}}. \tag{5.1.10}$$

If we now introduce the following combination of parameters

$$r := \frac{B_1 + B_2\alpha_2}{B_2\alpha_1 + B_3}, \qquad E := \frac{A_1}{B_2\alpha_1 + B_3} + \frac{A_2}{C_2\alpha_1 + C_3}, \tag{5.1.11}$$

Then it follows (solving (5.1.10)) that

$$I_2^m = \frac{p^m - \alpha_2 - \dfrac{r}{E}}{\dfrac{1}{E} + \alpha_1 + 1} = \frac{E\big(p^m - \alpha_2\big) - r}{1 + E\big(\alpha_1 + 1\big)}. \tag{5.1.12}$$

The substitution of (5.1.12) into (5.1.7) yields the desired result.

$$I_1^m = \frac{\alpha_1\left(Ep^m - r\right) + \alpha_2(1 + E)}{1 + E\big(\alpha_1 + 1\big)}. \tag{5.1.13}$$

Therefore, we have established the following result

Theorem 5.1.2. *Let α_i, r, and E be defined as in (5.1.8) and (5.1.11) respectively. Then if*

(H1a) $$\Big(1 + E\big(\alpha_1 + 1\big)\Big)\Big(E\big(p^m - \alpha_2\big) - r\Big) > 0,$$

and

(H1b) $$\Big(1 + E\big(\alpha_1 + 1\big)\Big)\Big(\alpha_1\big(Ep^m - r\big) + \alpha_2\big(1 + E\big)\Big) > 0,$$

there is a unique positive endemic equilibrium, and if

$$\Big(1 + E\big(\alpha_1 + 1\big)\Big)\Big(E\big(p^m - \alpha_2\big) - r\Big) \leq 0,$$

or

$$\Big(1 + E\big(\alpha_1 + 1\big)\Big)\Big(\alpha_1\big(Ep^m - r\big) + \alpha_2\big(1 + E\big)\Big) \leq 0,$$

then there is no positive endemic equilibrium.

5.2. Stability of The Positive Endemic Equilibrium.

We need the following two lemmas in order to establish our stability results.

Lemma 5.2.1. *The matrices*

$$P = \begin{pmatrix} A & B \\ C & D \end{pmatrix} \quad \text{and} \quad \bar{P} = \begin{pmatrix} A & -B \\ -C & D \end{pmatrix}$$

have the same eigenvalues.

The proof is trivial.

Lemma 5.2.2. *Let A be an $n \times n$ matrix whose diagonal elements are negative and off-diagonal elements are nonnegative. Let A_{1k} be the leading principal submatrix with k rows. Assume $(-1)^k \det A_{1k} > 0$, for $1 \leq k \leq n-1$. Then*

i) If $(-1)^n \det A = (-1)^n \det A_{1n} > 0$, A is stable; that is, all eigenvalues of A have negative real parts.

ii) If $\det A = 0$, there is a unique zero eigenvalue of A. The other eigenvalues all have negative real parts.

iii) If $(-1)^n \det A < 0$, there is a unique positive eigenvalue of A. The other eigenvalues all have negative real parts.

Proof.

i) Follows from the theory of M-matrices.

ii) We only prove this in the case when n is even. The proof is similar when n is odd.

Because $\det A_{1n-1} < 0$ then the first $n-1$ columns are linearly independent, which implies the uniqueness of the zero eigenvalue. Secondly, we consider matrix B defined by

$$B = A + \begin{pmatrix} 0 & 0 \\ 0 & -\epsilon \end{pmatrix},$$

where ϵ is a small positive number such that

$$\det B = -\epsilon \det A_{1n-1} + \det A = -\epsilon \det A_{1n-1} > 0$$

. Thee theory of $M-$matrices implies that all the eigenvalues of B have negative real parts. We complete the proof via a continuity argument, that is, we let ϵ approach zero. There is an eigenvalue reaching zero but this eigenvalue is unique from i). Hence the real parts of the other eigenvalues remain negative.

iii) The conclusion follows using the same approach used in ii).

Based on Lemmas 5.2.1 and 5.2.2, the stability of the coexistence equilibrium can be stated as follows:

Theorem 5.2.3. *The coexistence equilibrium* $E^* := \Big(I_1^m > 0, I_2^m > 0, I_1^f > 0, I_2^f > 0,$ $I_1^c > 0, I_2^c > 0)$, *give by (5.1.3), (5.1.4), (5.1.12), and (5.1.13) is asymptotically stable if the determinant of the following matrix*

$$J^* = \begin{pmatrix} j_{11} & j_{12} & j_{13} & j_{14} & 0 & 0 \\ j_{21} & j_{22} & 0 & 0 & j_{25} & 0 \\ j_{31} & 0 & j_{33} & 0 & 0 & j_{36} \\ j_{41} & 0 & 0 & j_{44} & j_{45} & j_{46} \\ 0 & j_{52} & 0 & j_{54} & j_{55} & 0 \\ 0 & 0 & j_{63} & j_{64} & 0 & j_{66} \end{pmatrix}$$

where

$$j_{11} := -\sigma_1^m - G_1,\ j_{12} := \frac{\sigma_1^m a_1^m I_1^m}{G_1},\ j_{13} := \frac{\sigma_1^m a_1^{mc} I_1^m}{G_1},$$

$$j_{14} := G_1,\ j_{21} := \frac{\sigma_1^f I_1^f}{I_1^m},\ j_{22} := -\sigma_1^f - a_1^f I_1^m,\ j_{25} := a_1^f I_1^m,\ j_{31} := \frac{\sigma_1^c I_1^c}{I_1^m},$$

$$j_{33} := -\sigma_1^c - a_1^c I_1^m,\ j_{36} := a_1^c I_1^m,\ j_{41} := G_2,\ j_{44} := -\sigma_2^m - G_2,$$

$$j_{45} := \frac{\sigma_2^m a_2^m I_2^m}{G_2},\ j_{46} := \frac{\sigma_2^m a_2^{mc} I_2^m}{G_2},\ j_{52} := a_2^f I_2^m,\ j_{54} := \frac{\sigma_2^f I_2^f}{I_2^m},$$

$$j_{55} := -\sigma_2^f - a_2^f I_2^m,\ j_{63} := a_2^c I_2^m,\ j_{64} := \frac{\sigma_2^c I_2^c}{I_2^m},\ j_{66} := -\sigma_2^c - a_2^c I_2^m,$$

with

$$G_1 := a_1^m I_1^f + a_1^{mc} I_1^c. \qquad G_2 := a_2^m I_2^f + a_2^{mc} I_2^c.$$

evaluated at E^* is positive. Furthermore, if the determinant of J^* is negative then the stable manifold and the unstable manifold of the system at E^* are five-dimensional and one-dimensional respectively.

Proof. Denote the leading principal minors of J^* with i rows by J_i^*. Then, by tedious algebraic manipulations,

$$J_2^* = \frac{\sigma_1^m \sigma_1^f a_1^{mc} I_1^c}{G_1} + \sigma_1^m a_1^f I_1^m + \left(\sigma_1^f + a_1^f I_1^m\right) G_1 > 0,$$

$$J_3^* = -\frac{\sigma_1^m \sigma_1^c a_1^m a_1^f I_1^m I_1^f}{G_1} - \sigma_1^m a_1^f a_1^c I_1^m I_1^m - (\sigma_1^c + a_1^c I_1^m)\left(\sigma_1^f + a_1^f I_1^m\right) G_1 < 0,$$

$$J_4^* = -\sigma_2^m H_{13} + G_2 \left(\frac{\sigma_1^m \sigma_1^c a_1^m a_1^f I_1^m I_1^f}{G_1} + \sigma_1^m a_1^f a_1^c I_1^m I_1^m \right) > 0,$$

and

$$\begin{aligned} J_5^* = &- \sigma_1^c \left(\sigma_2^m \sigma_2^f a_2^m (\sigma_1^f + a_1^f I_1^m) I_2^c \frac{G_1}{G_2} - \sigma_1^f \sigma_2^m a_1^{mc} a_2^f I_1^c I_2^m - \frac{\sigma_1^m \sigma_2^m \sigma_2^f a_1^m a_1^f a_2^{mc} I_1^m I_1^f I_2^c}{G_1 G_2} \right) \\ &- a_1^c I_1^m \left\{ \frac{\sigma_1^m \sigma_1^f \sigma_2^m \sigma_2^f a_1^{mc} a_2^{mc} I_1^c I_2^c}{G_1 G_2} + \frac{\sigma_1^m \sigma_1^f a_1^{mc} I_1^c}{G_1} (\sigma_2^f + (1+\sigma_2^m) a_2^f I_2^m) \right. \\ &+ \frac{\sigma_2^m \sigma_2^f a_2^{mc} I_2^c}{G_2} (\sigma_1^f + (1+\sigma_1^m) a_1^f I_1^m) + \sigma_1^f \sigma_2^m a_1^{mc} a_2^f I_1^c I_2^m \\ &\left. + \sigma_1^m \sigma_2^f a_1^f a_2^{mc} I_1^m I_2^c + \sigma_1^m a_1^f a_2^f I_1^m I_2^m G_2 \right\} < 0. \end{aligned}$$

Since the determinant of J^* is positive then from Lemma 5.2.2 it follows that all the eigenvalues of J^* have negative real parts and, therefore, E^* is stable. If the determinant of J^* is negative then J^* has five eigenvalues with negative real parts and one positive eigenvalue. Hence, the rest of the conclusions of the theorem follow.

We end this section with two examples.

Example 1 Set the following set of parameters:

$$\begin{array}{llllll} \mu = 0.025, & \mu^c = 0.025, & \Lambda^m = \Lambda^f = 1000, & b^m = 6, & b^f = 4, & b^c = 4, \\ \beta_1^m = 0.25, & \beta_2^m = 0.2, & \beta_1^f = 0.05, & \beta_2^f = 0.1, & \beta_1^c = 0.05, & \beta_2^c = 0.1, \\ \gamma_1^m = 0.02, & \gamma_2^m = 0.1, & \gamma_1^f = 0.02, & \gamma_2^f = 0.6, & \gamma_1^c = 0.7, & \gamma_2^c = 0.03. \end{array}$$

$$\Big(1 + E(\alpha_1 + 1)\Big)\Big(E(p^m - \alpha_2) - r\Big) = 1982582,$$

and

$$\Big(1 + E(\alpha_1 + 1)\Big)\Big(\alpha_1(Ep^m - r) + \alpha_2(1 + E)\Big) = 3877073.$$

Then, (H1) is satisfied and hence, there exists a positive equilibrium. In fact, this endemic equilibrium can be determined numerically as

$$\begin{array}{lll} I_1^m = 24156, & I_1^f = 36233, & I_1^c = 2634, \\ I_2^m = 12352, & I_2^f = 1067, & I_2^c = 14204. \end{array}$$

Since $\det J^* = 0.004$ then Theorem 5.2.3 implies the asymptotic stability of the coexistence equilibrium. This can be confirmed numerically by a direct computation of the eigenvalues of H^* which are

$$\begin{array}{lll} \lambda_1 = -1.46, & \lambda_2 = -0.38, & \lambda_3 = -1.98, \\ \lambda_4 = -0.84, & \lambda_5 = -0.37, & \lambda_6 = -1.17. \end{array}$$

The two female groups have different recovery rates or incubation periods to the two strains. More specifically, females in group f with strain 1 have a longer incubation period or need longer time to recover than females in group c infected with strain 1. However the situation is reversed for strain 2, namely, females in group c with strain 2 have a longer incubation period than their counterparts from group f. We can also interpret these differences in γ_i^k not as directly linked to the incubation period distributions but rather to the ability of these strains to conceal themselves (asymptomatic individuals) in different populations to "retard" treatment. In this example, females in

group f with strain 1 and in group c with strain 2 can be thought as having the longer strain-specific asomptomatic periods.

Because (H1) is satisfied, it follows from Theorem 5.1.2 that there exists a positive endemic equilibrium. However, it may be unstable.

Example 2 We now use the following set of parameters:

$$\begin{array}{llllll} \mu = 0.025, & \mu^c = 0.015, & \Lambda^m = 200, & \Lambda^f = 100, & & \\ b^m = 4, & b^f = 2, & b^c = 4, & & & \\ \beta_1^m = 0.24, & \beta_2^m = 0.2, & \beta_1^f = 0.05, & \beta_2^f = 0.1, & \beta_1^c = 0.4, & \beta_2^c = 0.15, \\ \gamma_1^m = 0.15, & \gamma_2^m = 0.08, & \gamma_1^f = 0.1, & \gamma_2^f = 0.15, & \gamma_1^c = 0.15, & \gamma_2^c = 0.1. \end{array}$$

Then

$$\Big(1 + E(\alpha_1 + 1)\Big)\Big(E(p^m - \alpha_2) - r\Big) = 1859598,$$

and

$$\Big(1 + E(\alpha_1 + 1)\Big)\Big(\alpha_1(Ep^m - r) + \alpha_2(1 + E)\Big) = 1110.$$

Hence, the coexistence equilibrium exists and its components are

$$\begin{array}{lll} I_1^m = 8.6, & I_1^f = 0.6, & I_1^c = 6.7, \\ I_2^m = 14318.4 & I_2^f = 549.8, & I_2^c = 13435.2. \end{array}$$

However, since $\det H = -0.8 \times 10^{-7}$, it follows from Theorem 5.2.3 that this coexistence equilibrium is unstable and the unstable manifold is one dimensional. The corresponding set of eigenvalues of H,

$$\begin{array}{lll} \lambda_1 = -0.95, & \lambda_2 = -0.78, & \lambda_3 = -0.32, \\ \lambda_4 = -0.12, & \lambda_5 = -0.5, & \lambda_6 = 0.5 \times 10^{-5}, \end{array}$$

corroborates our conclusion.

In one-sex models as studied in Blythe et. al (1993), whenever a coexistence equilibrium exists, it is always stable. This is not the case for our two-sex model. Hence, a heterosexual structure may have a destabilizing effect on coexistence.

6. Concluding Remarks

An important principle in theoretical biology is that of competitive exclusion which states that *no two species can forever occupy the same ecological niche.* Clarifications on the meaning of competitive exclusion and niche have been central to theoretical ecology (Butler et al., 1983; Levin, 1970; May 1975; Maynard Smiths, 1974). Sexually-transmitted diseases like gonorrhea have incredibly high incidences throughout the world providing the necessary environment and opportunities for the evolution of new strains (see Hethcote and Yorke, 1984, and references therein). The co-existence of gonorrhea strains is becoming an increasingly serious problem. Understanding the mechanisms that lead to co-existence or competitive exclusion is central to the development of disease management strategies as well as to our increase understanding of STD-dynamics.

We previously formulated heterosexual models where two strains or any number of strains competed for "identical" hosts becausewe included only one homogeneous female group in the population. The outcome of these models was always the same: competitive exclusion (Castillo-Chavez, Huang, and Li, 1993, 1994). In this article, we study a heterosexual model where two "genetically" different female groups interact with a homogeneous (genetically uniform) male population in the presence of two competing strains of a venereal disease. We have found out that, under various situations, both competitive exclusion and coexistence may occur. We saw that as expected, the strain with higher transmissibility (in all groups) or the strain to which *both* female groups are more suceptible (if such is the case) then we have competitive exclusion. Mathematically, the result follows from the inequalities $R_i^m R_i^f > R_j^m R_j^f$ and $R_i^m R_i^c > R_j^m R_j^c$. Strain i wins and strain j loses.

On the other hand, if the transmissibility of one strain is higher, let's say in group f

than group c then the transmissibility must be reversed for the other strain to make co-existence likely. A similar level of asymmetry must exist between both group of females regarding their average periods of infection (or their average asymptomatic periods) to increase the likelihood of coexistence. Tne necessary conditions for coexistence require that inequalities like $R_i^m R_i^f > R_j^m R_j^f$ and $R_i^m R_i^c < R_j^m R_j^c$ be satisfied. Coexistence is possible only under a set of complex relationships between these factors as illustrated in the examples. Furthermore, we observe that the existence of a co-existence equilibrium did not guarantee its stability.

It is clear to us that the limited heterogeneity available in our system makes the meeting of the conditions for coexistence difficult. It is even more difficult to meet the conditions for stabel co-existence. We have been unable to provide transparent and specific necessary and sufficient *biological* conditions guaranteeing stable co-existence in our system. Nevertheless, it is important to re-iterate a key feature of our investigations, that coexistence is indeed theoretically possible as soon as a *minimal* level of diversity is introduced. Preliminary results show that superinfection as defined in the works of Levin (1981, 1983a,1983b) provides a clear *biological* mechanism for co-existence. We will concentrate our efforts in elucidating the role of superinfection as a mechanism that supports a pathogens' diversity in a *minimally* heterogeneous host population.

Acknowledgment. This research was partially supported by NSF grant DEB-925370, Presidential Faculty Fellowship Award. to Carlos Castillo-Chavez, by the Center for Applied Mathematics at Cornell University, and by the U.S. Army Research Office through the Mathematical Sciences Institute of Cornell University (Contract DAAL03-91-C-0027).

REFERENCES

Anderson, R. M., and R. M. May (1982) *Co-evolution of host and parasites*, Parasitology, 85: 411–426.

Anderson, R. M., and R. M. May (1991) Infectious Diseases of Humans, Oxford Science Publications, Great Britain.

Beck, K., (1984) *Co-evolution. Mathematical aspects of host-parasite interactions*. J. Math. Biol., 19: 63–77.

Blythe, S. P., F. Brauer, C. Castillo-Chavez, and J. X. Velasco-Hernández (1993) *Sexually transmitted diseases with recruitment*, Biometrics Unit Technical Report BU-1193-M, Cornell University.

Blythe, S., Castillo-Chavez, C., Wenzhang Huang, and Jia Li, (1994) *On coexistence of pathogen in a class of sexually-transmitted disease models*, (preprint)

Brauer, F., S. P. Blythe, C. Castillo-Chavez (1992) *Demographic recruitment in sexually transmitted disease models*, Biometrics Unit Technical Report BU-1154-M, Cornell University.

Bremermann, H. J. and J. Pickering, (1983) *A game-theoretical model of parasite virulence*, J. Theor. Biol., 100: 411–426.

Bremermann, H. J. and H. R. Thieme (1989) *A competitive exclusion principle for pathogen virulence*, J. Math. Biol., 27: 179–190.

Busenberg, S and C. Castillo-Chavez (1989) *Interaction, pair formation, and force of infection terms in sexually transmitted diseases*, In: Mathematical and Statistical Approaches to AIDS Epidemiology (C. Castillo-Chavez, ed.), Lect. Notes in Biomath., Vol 19, Springer-Verlag, Berlin, pp. 63–77.

Busenberg, S and C. Castillo-Chavez (1991) *A general solution of the problem of mixing of subpopulations, and, its application to risk- and age-structured epidemic models*, IMA J. Math. Appl. Med. Biol., 8: 1–29.

Buttler, G. J., S. B. Hsu and P. Waltman (1983) *Coexistence of competing predators in a chemostat*, J. Math. Biol., 17: 133–151.

Castillo-Chavez, C., ed. (1989) Mathematical and Statistical Approaches to AIDS Epidemiology, Lect. Notes Biomath. 83. Springer-Verlag, New York.

Castillo-Chavez, C., K. Cooke, W. Huang and S. A. Levin (1989a) *Results on the dynamics for models for the sexual transmission of the human immunodeficiency virus,* Applied Math. Letters, 2(4): 327–331.

Castillo-Chavez, C., H. W. Hethcote, V. Andreasen, S. A. Levin and Wei-min Liu (1988) *Cross-immunity in the dynamics of homogeneous and heterogeneous populations,* in: Mathematical Ecology (T. G. Hallam, L. G. Gross, and S. A. Levin, eds.), 303-316, World Scientific Publishing Co., Singapore.

Castillo-Chavez, C., H. W. Hethcote, V. Andreasen, S. A. Levin and Wei-min Liu (1989) *Epidemiological models with age structure, proportionate mixing, and cross-immunity,* J. Math. Biol., 27: 233–258.

Castillo-Chavez, C., Wenzhang Huang, and Jia Li (1993) *Competitive exclusion in gonorrhea models and other sexually-transmitted diseases,* (to appear in SIAM J. Appled Math.)

Castillo-Chavez, C., Wenzhang Huang, and Jia Li (1994) *Dynamics of multiple pathogen strains in heterosexual epidemiological models,* (preprint)

Castillo-Chavez, C. and H. R. Thieme (1994) *Asymptotically autonomous epidemic models,* In: Proc. Third Intern. Conf. on Mathematical Population Dynamics (O. Arino and M. Kimmel, eds.) (in press)

Castillo-Chavez, C., J. X. Velasco-Hernàndez, and S. Fridman (1994) *Modeling Contact Structures in Biology.* In: Frontiers of Theoretical Biology (S. A. Levin, ed.), Lect. Notes in Biomath., Vol. 100, Springer-Verlag, Berlin. (in press)

Cooke, K. L. and J. A. Yorke (1973) *Some equations modelling growth processes and gonorrhea epidemics,* Math. Biosci., 58: 93–109.

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

Dietz, K. (1979) *Epidemiologic interference of virus populations,* J. Math. Biol., 8: 291–300.

Dwyer, G., S.A. Levin, and L. Buttel (1990) *A simulation model of the population dynamics and evolution of myxomatosis,* Ecological Monographs, 60: 423–447.

Ewald, W. P. (1993) *The evolution of virulence,* Scientific American, April: 86–93.

Ewald, W. P. (1994) Evolution of Infectious Disease, Oxford University Press, Oxford.

Heesterbeek, H. (1992) R_0, Thesis, CWI, Amsterdam.

Fenner, F. and K. Myers (1978) *Myxoma virus and myxomatosis in retrospect: the first*

quarter century of a new disease, in: Viruses and the Environment (J.I. Cooper and F.O. MacCallum, eds.), 539–57 0, Academic Press, London.

Fenner, F. and F. N. Ratcliffe (1965) Myxomatosis, Cambridge University Press, Cambridge.

Fiedler, M. and V. Pták (1962) *On matrices with non-positive off-diagonal elements and positive principal minors,* Czechoslovak Math. J., 12: 382–400.

Hethcote, H. W., and J. A. Yorke (1984) *Gonorrhea Transmission Dynamics and Control,* Lect. Notes Biomath. Vol. 56. Springer-Verlag, New York.

Hsu Schmitz, S-F (1993) Some Theories, Estimation Methods and Applications of Marriage Functions in Demography and Epidemiology, PhD dissertation, Cornell University.

Huang, W., K. Cooke and C. Castillo-Chavez (1992) *Stability and bifurcation for a multiple group model for the dynamics of HIV/AIDS transmission,* SIAM J. of Applied Math. 52: 835–854.

Lajmanovich, A. and J. A. Yorke (1976) *A deterministic model for gonorrhea in a nonhomogeneous population,* Math. Biosci., 28: 221–236.

Levin, S. A. (1970) *Community equilibria and stability, and an extension of the competitive principle exclusion,* Am. Naturalist, 104: 413–423.

Levin, S. A. (1983a) *Co-evolution,* In: Population Biology (H. I. Freedman and C. Strobeck, eds.), Lect. Notes Biomath. Vol. 52, Springer-Verlag, New York.

Levin, S. A. (1983b) *Some approaches to the modeling of co-evolutionary interactions,* In: Co-evolution (M. Nitecki, ed.), University of Chicago Press, Chicago.

Levin, S. A. and D. Pimentel (1981) *Selection of intermediate rates increase in parasite-host systems,* Am. Naturalist, 117: 308–315.

Lotka, A. J. (1923) *Contributions to the analysis of malaria epidemiology,* Am. J. Hyg., 3: Jan. Suppl.

May, R. M. (1975) Stability and Complexity in Models Ecosystems, Princeton University Press, Princeton, N. J.

May, R. M. and R. M. Anderson (1983) *Epidemiology and genetics in the co-evolution of parasites and hosts,* Philos. Trans. R. Soc. Lond., B, 219: 281–313.

May, R. M. and R. M. Anderson (1990) *Parasite-host coevolution,* Parasitology 100: S89–S101.

Maynard Smith, J. (1978) The Evolution of Sex, Cambridge University Press, Cambridge, Great Britain.

Poole, G. and T. Boullion (1974) *A survey on M-matrices,* SIAM Review, 16: 419–427.

Ross, R. (1911) The Prevention of Malaria, 2nd ed., (with Addendum), John Murray, London.

Smith, H. L. (1988) *Systems of ordinary differential equations which generate an order preserving flow. A survey of results*, SIAM Rev. 30: 87–113.

Thieme, H.R. (1992) *Convergence results and a Poincaré-Bendixson tricho-tomy for asymptotically autonomous differential equations*, J. Math. Biol., 30: 755-763.

Thieme, H. R. (1994) *Asymptotically autonomous differential equations in the plane*, Rocky Mountain J. Math. 24: 351–380.