DISEASE TRANSMISSION IN MULTIGROUP POPULATIONS OF VARIABLE SIZE

by

S. BUSENBERG & P. VAN DEN DRIESSCHE

DMS-620-IR October 1992

Disease Transmission in Multigroup Populations of Variable Size

April 11, 1993

Stavros Busenberg[1] and P. van den Driessche[2]

[1] Department of Mathematics
Harvey Mudd College
Claremont, CA 91711
USA

[2] Department of Mathematics and Statistics
University of Victoria
Victoria, B.C.
Canada V8W 3P4

Abstract

The interactions between demography and epidemics are investigated for the transmission of diseases in populations which have an arbitrary number of distict epidemiological groups. The existence and stability of a disease free equilibrium is obtained and various threshold criteria which determine the course of the spread of the disease are derived. Implications of the interactions of the demographic and disease transmission processes are discussed, and epidemiological interpretations are given for the different threshold criteria which govern the spread of the disease.

[1] Research supported in part by NSF grant DMS-9112821.

[2] Research supported in part by NSERC Operating Grant A-8965 and the Bilateral Exchange Program.

Please address correspondence regarding this paper to:

P. van den Driessche, Department of Mathematics and Statistics, University of Victoria, Victoria, B.C., Canada V8W 3P4.
e-mail: PVDD@UVVM.UVIC.CA FAX: (604) 721-8962.

Disease Transmission in Multigroup Populations of Variable Size

Stavros Busenberg[1] *and P. van den Driessche*[2]

[1] Department of Mathematics, Harvey Mudd College, Claremont, California 91711
[2] Department of Mathematics and Statistics, University of Victoria, Victoria, B.C., Canada V8W 3P4

1 Introduction

The transmission of communicable diseases in animal populations involves various types of interactions between individuals carrying the pathogens that cause the disease and those susceptible to new infection. There are various characteristics of individuals which affect both their propensity to interact with each other, and the likelihood of an interaction leading to the transmission of a disease. These characteristics may include social and economic status, age, profession, and a variety of other distinctions which affect interactions with others in the given population. The structuring of a population due to age differences has been an integral part of two of the pioneer epidemic models due to Bernoulli (1760) and McKendrick (1926), and this type of modelling continues to be used (see, for example, Busenberg, Cooke and Iannelli (1988), and the references therein). Most of the classical models of epidemics have tended to neglect other natural epidemiological groupings of populations.

However, in the more recent literature on mathematical epidemiology there are many models which include the effects of different internal structures of the population on the dynamics of disease transmission (see, for example, Lajmanovich and Yorke (1976), Hethcote (1978), Travis *et al.* (1980), Hethcote and Yorke (1984), Anderson and May (1985), Hethcote and Thieme (1985), Sattenspiel (1987), Hethcote and Van Ark (1987), Busenberg and Cooke (1988), Jacquez *et al.* (1988), Sattenspiel and Simon (1988), Castillo-Chavez *et al.* (1989)). Most of this work is concerned with populations of a fixed total size, a condition which is a reasonable approximation only for diseases which have a short duration in comparison with the time scale of the natural changes in total population size. The data for human populations in underdeveloped countries in particular, indicate that this type of steady-state assumption should not be taken as a valid approximation for any disease which involves multiyear incubation or infectivity periods. One example of such a disease which is widely being studied at present is

HIV/AIDS. Serious attempts to find the interplay between variations of population size and the dynamics of this disease include the work of Anderson, May and McLean (1988), Brauer (1990, 1991), Busenberg, Cooke and Pozio (1983), Busenberg, Cooke and Thieme (1991), and Pugliese (1990). In the modelling of insect populations which often act as vectors of human infections, it is seldom the case that the populations can be regarded as being of constant size within the time scale of the dynamics of disease transmission. Models of vector borne diseases, such as the ones in Busenberg and Cooke (1982, 1988), include this interplay between the disease and the population dynamics; and in their model of host parasite dynamics with multi-stage infective agents, Bremermann and Thieme (1989) assume the host population has limited growth.

The purpose of the present paper is to study the dynamic effects of diseases in populations which are not in a steady state situation, and which are divided into multiple subpopulations with distinct disease transmission properties. We derive and analyze a model that describes this type of disease transmission, using a proportionate mixing force of infection term. There are clear problems in extending the widely accepted proportionate mixing force of infection term to populations with varying sizes. We show how to allow the transmission dynamics of the disease for any population subgroup to be caused by more than one mechanism. This can occur, for example, when an individual faces disease transmission conditions at the workplace which differ from those at other social interactions. This "mixing" of the types of the force of infection terms, albeit in constant total populations, has been studied by Nold (1980) and by Andreasen and Christiansen (1989), among others. We show that only certain forms of the force of infection allow for the possibility that endemic proportions can reach steady states when the total population is varying in size. We analyze in detail the dynamic behavior of our model and show that there is a unique disease free equilibrium. We derive linear stability criteria for this disease free state, provide threshold criteria, and obtain conditions under which the total number of infectives either tend to zero or grow when their proportion is constant in a growing population. We also discuss the existence of an endemic proportion steady state. We show that the stability and threshold criteria can be different depending on whether or not the total population is increasing or decreasing. This occurs in other disease transmission models which account for changes of population size (see Anderson, May, and McLean (1988), Busenberg, Cooke and Pozio (1983), Busenberg, Cooke and Thieme (1991), Busenberg and van den Driessche (1990), Busenberg and Hadeler (1990), Busenberg and Vargas (1991), and Gao and Hethcote (1992)).

We now turn to the discussion of the force of infection term in a multigroup population of varying size. Consider a population that is subdivided into n discrete subpopulations which interact with each other in different ways. Assume that within each of these groups there are three epidemiologically distinct types of individuals, the susceptibles, the infectives, and the removeds. Total numbers in subgroup j are respectively denoted by S_j, I_j, and R_j. We deal with a model which is, within each subpopulation group, of the $S_j \to I_j \to R_j \to S_j$ type. The total population of group j, denoted by N_j, is given by $N_j = S_j + I_j + R_j$, and is allowed to vary with time. We assume that there are three basic modes for disease transmission within each group and between different groups.

The first mode of transmission does not involve direct person to person contact, but rather contact with a common environment, such as food or air. In this circumstance, each infective adds to the general pathogen load of the environment and the force of infection is proportional to the total number of infectives, perhaps with some saturation level occurring when the number of infectives becomes very large (see Capasso and Serio (1978)). Neglecting this saturation at high infective numbers, the force of infection on susceptibles of group j, takes a *mass-action* form of the type:

$$\sum_k \lambda_{jk} I_k, \tag{1.1}$$

where $\lambda_{jk} = K_{jk} c_j$, K_{jk} is the per capita contribution of pathogen by an infective of group k to the environment of group j; and c_j is the rate at which a susceptible from group j comes into a disease transmitting contact with the affected environment. Unless indicated otherwise, our summations are over all groups, so k varies from 1 to m in (1.1).

The second mode of transmission that we consider involves personal contacts between individuals. Such contacts are assumed to occur at random between all individuals in the total population, but the nature of the contacts, as far as the probability for disease transmission is concerned, varies with the group. The force of infection term in this case takes the form

$$\sum_k \lambda_{jk} \frac{I_k}{N}, \tag{1.2}$$

where λ_{jk} has the same form as above, however, with K_{jk} now being the proportion of contacts between an infective of group k and a susceptible of group j which leads to an infection, and c_j being the rate at which a single susceptible of group j has contacts with other individuals in the total population $N = \sum_k N_k$. The proportion I_k/N of these contacts is with infectives of group k, thus the rate at which the infection is being transferred to group j individuals, due to such contacts, is given by the k^{th} term in (1.2). We call this type of force of infection term *total proportionate mixing*, in order to distinguish it from the more general *proportionate mixing* terms that we discuss below. Most of the detailed analysis in this paper deals with the form (1.2) for the force of infection.

The third type of disease transmission that we consider involves direct contacts between individuals in the population. As discussed in Jacquez *et al.* (1988) in their model of HIV transmission, where there is a nonconstant but bounded population, and in Andreasen and Christiansen (1989) for person to person contact situations, the proportionate mixing hypothesis leads to interaction terms of the form

$$c_j \sum_k L_{jk} \frac{c_k I_k}{\sum_m c_m N_m}, \tag{1.3}$$

where c_k represents the rate at which members of group k make contacts with other members in the population. Here L_{jk} is the proportion of those contacts of members of group k which are with members of group j. Now, letting K_{jk} be the proportion of

contacts between an infective of group k with a susceptible of group j which lead to the transmission of the infection, we obtain the following form for the force of infection in this case:

$$\sum_k \lambda_{jk} \frac{c_k I_k}{\sum_m c_m N_m}, \tag{1.4}$$

where $\lambda_{jk} = K_{jk} L_{jk} c_j$. We note that, if the c_j are all equal in (1.4), then the proportionate mixing force of infection reduces to the total proportionate mixing term given in (1.2).

A more general form of the force of infection which includes both (1.1) and (1.2) is given by

$$\sum_k \lambda_{jk} \frac{I_k}{N^{\zeta_k}}, \tag{1.5}$$

with $\zeta_k \in [0,1]$. Note that this form reduces to (1.1) when $\zeta_k = 0$, and to (1.2) when $\zeta_k = 1$. We shall return to this form in what follows. It is important to note that the units of the λ_{jk} are different depending on the form of the force of infection term that is used. For (1.2) and (1.4), the units of λ_{jk} are $1/(time)$, while for (1.1) they are $1/(time \times person)$. In the general form (1.5) the units of λ_{jk} are $1/(time \times person^{1-\zeta_k})$. If all three types of contacts, (1.2), (1.3), and (1.4), are present, then the form of the force of infection becomes:

$$\sum_k \left[\lambda_{jk}^{(1)} + \frac{\lambda_{jk}^{(2)}}{N} + \frac{c_k \lambda_{jk}^{(3)}}{\sum_m c_m N_m} \right] I_k. \tag{1.6}$$

Since direct contacts between susceptibles and infectives occur between pairs of individuals, there is a natural symmetry condition that needs to be imposed on the coefficients which enter through λ_{jk} in (1.2) and (1.4). Dealing with (1.2) first, we note that the total number of contacts per unit time (say per day) of susceptibles from group j with infectives of group k is given by $c_j S_j I_k / N$. If c_k^* denotes the rate of contact between one infective of group k and other individuals in the population, we have

$$c_k^* I_k S_j / N = c_j S_j I_k / N.$$

Thus, we must have $c_j = c_k^*$, for all j and k. Consequently, c_j cannot depend on the group index j. Thus, the λ_{jk} vary with j and k only because there is a difference in the probability of transmission of the disease, given that a contact has occurred between a susceptible member of one group and an infective of another. We note that λ_{jk} need not be symmetric in j and k, since individuals from different groups may have widely differing susceptibilities of acquiring an infection upon contact with an infective from another group.

In the case of the proportionate mixing terms in equations (1.3) and (1.4), the same symmetry of contacts reasoning applies as for (1.2), and it results in the condition

$$c_k c_j L_{kj} S_j I_k = c_j c_k L_{jk} I_k S_j,$$

thus, $L_{kj} = L_{jk}$. However, $\lambda_{jk} = K_{jk}L_{jk}c_j$ is not necessarily symmetric in j and k. Note that the above restriction does not apply to the coefficients c_k in (1.1) since, in that situation, the disease is not being transmitted via direct person to person contacts. The λ_{jk} once again need not be symmetric in j and k.

Each term of the more general form given by (1.5) can be written as the product

$$\left(\frac{K_{jk}L_{jk}}{N^{\zeta_k-1}}\right)\left(c_j\frac{I_k}{N}\right), \tag{1.7}$$

from which it is seen that the coefficient $\left(\frac{K_{jk}L_{jk}}{N^{\zeta_k-1}}\right)$ can be viewed as representing the proportion of contacts between susceptibles with infectives (in a proportionate mixing situation) which lead to transfer of the disease from the infective to the susceptible individual. The nonlinear dependence of this term on the total population may reflect behavioral changes that occur when the total population size varies and which affect disease transmission.

2 Model Formulation

We now formulate our m-group $S_j \to I_j \to R_j \to S_j$ model with total proportionate mixing. We assume that the births in each group are proportional to the total population number, but with a different birth rate in each group. The parameters, assumed nonnegative, are

b_j = birth rate in group j, assumed positive,
d_j = natural death rate in group j, assumed positive,
λ_{jk} = effective contact rate,
γ_j = recovery rate in group j, assumed positive,
β_j = rate of loss of immunity in group j,
ϵ_j = excess death rate in infective class in group j,
δ_j = excess death rate in removed class in group j.

The rate of change of each class in group j, $j = 1, \ldots, m$, is given by

$$S_j' = b_j N - d_j S_j - S_j \sum_k \lambda_{jk} I_k/N + \beta_j R_j, \tag{2.1}$$

$$I_j' = -(d_j + \epsilon_j)I_j - \gamma_j I_j + S_j \sum_k \lambda_{jk} I_k/N, \tag{2.2}$$

$$R_j' = -(d_j + \delta_j)R_j + \gamma_j I_j - \beta_j R_j. \tag{2.3}$$

Here $N = \sum_j (S_j + I_j + R_j) = \sum_j N_j$ and unless indicated otherwise, summations are over all groups, so the index runs from 1 to m. Adding these gives the equation for the total population

$$N' = bN - \sum_j (d_j N_j + \epsilon_j I_j + \delta_j R_j), \tag{2.4}$$

where $b = \sum_j b_j$. It is easy to see that, for given nonnegative initial data, the model is well posed and has nonnegative solution for all subsequent time.

The special case of a 1-group model is completely analyzed in Busenberg and van den Driessche (19). As in that case, with a variable population size, we work with *proportions* of the population. Thus we define

$$s_j = S_j/N, \qquad i_j = I_j/N, \qquad r_j = R_j/N, \qquad n_j = N_j/N,$$

and so $n_j = s_j + i_j + r_j$ is the proportion of the total population in a group j. Then the model equations become

$$s_j' = b_j + s_j \left[-d_j - b + \sum_k (d_k n_k + \epsilon_k i_k + \delta_k r_k - \lambda_{jk} i_k) \right] + \beta_j r_j, \tag{2.5}$$

$$i_j' = -i_j (d_j + \epsilon_j + \gamma_j + b) + i_j \sum_k (d_k n_k + \epsilon_k i_k + \delta_k r_k) + s_j \sum_k \lambda_{jk} i_k, \tag{2.6}$$

$$r_j' = -r_j (d_j + \delta_j + \beta_j + b) + \gamma_j i_j + r_j \sum_k (d_k n_k + \epsilon_k i_k + \delta_k r_k), \tag{2.7}$$

giving

$$n_j' = b_j - n_j (d_j + b) + n_j \sum_k (d_k n_k + \epsilon_k i_k + \delta_k r_k) - \epsilon_j i_j - \delta_j r_j. \tag{2.8}$$

Also, defining $i = \sum_j i_j$, we have an equation for the total proportion of infectives, namely

$$i' = -bi + \sum_j \left(i (d_j n_j + \epsilon_j i_j + \delta_j r_j) - i_j (d_j + \epsilon_j + \gamma_j) + s_j \sum_k \lambda_{jk} i_k \right). \tag{2.9}$$

3 Disease Free Equilibrium

The possible disease free equilibrium (DFE) steady-states with $s_j \geq 0$, $i_j = 0$ for all j, from (2.5) and (2.7), satisfy

$$0 = b_j + s_j \left[-d_j - b + \sum_k (d_k s_k + (d_k + \delta_k) r_k) \right] + \beta_j r_j, \tag{3.1}$$

and either $r_j = 0$, or

$$0 = -(d_j + \delta_j + \beta_j + b) + \sum_k (d_k s_k + (d_k + \delta_k) r_k). \tag{3.2}$$

We note that, since b_j is assumed > 0, by (3.1) we must have $s_j > 0$ for any DFE, and so

$$-d_j - b + \sum_k (d_k s_k + (d_k + \delta_k) r_k) < 0.$$

Thus (3.2) gives $0 < -(\beta_j + \delta_j)$ which is impossible. Thus $r_j = 0$ is the only possibility in a DFE, which means $s_j = n_j$. We have the following existence and uniqueness result.

Lemma 3.1 *If $b_j > 0$ for all j, then there exists a unique disease free equilibrium (DFE) for the model equations* (2.5)-(2.7). *The DFE $\bar{s} = (\bar{s}_1, \ldots, \bar{s}_m)^T$ satisfies*

$$\bar{i}_j = \bar{r}_j = 0, \quad 0 < \bar{s}_j \leq 1 \text{ for } j = 1, \ldots, m \text{ and } \sum_j \bar{s}_j = 1.$$

The $\bar{s}_j$ satisfy

$$b - \sum_k d_k \bar{s}_k = b_j/\bar{s}_j - d_j = b_1/\bar{s}_1 - d_1, \tag{3.3}$$

with the expressions in (3.3) *having the same sign as*

$$\sum_k b_k/d_k - 1,$$

and being equal to zero if and only if $\sum_k b_k/d_k = 1$. Moreover, $\bar{s}_1$ satisfies the equation

$$0 = b_1 + \bar{s}_1 \left[-d_1 - b + \bar{s}_1 \sum_k \frac{d_k b_k}{b_1 + (d_k - d_1)\bar{s}_1} \right]. \tag{3.4}$$

Proof. The proof that $r_j = 0$ for any steady state precedes the lemma statement. In the special case when $\sum_j b_j/d_j = 1$, then, for $m \geq 2$, $b_j/d_j < 1$ for all j. Thus $\bar{s}_j = \bar{n}_j = b_j/d_j$ and so (2.4) shows that the total population N is constant. When $r_j = 0$, $j = 1, \cdots, m$, condition (3.1) can be rewritten as the fixed point problem

$$\bar{s}_j = \frac{b_j}{b+h} + \bar{s}_j \left[\frac{-d_j + h}{b+h} + \sum_k \frac{d_k}{b+h} \bar{s}_k \right] \equiv F_j(\bar{s}) \tag{3.5}$$

where $h > d_j$ is a positive constant. As $\sum_j \bar{s}_j = 1$, we have

$$\sum_j F_j(\bar{s}) = \frac{b}{b+h} + \frac{h}{b+h} - \sum_j \frac{d_j \bar{s}_j}{b+h} + \sum_k \frac{d_k \bar{s}_k}{b+h} = 1.$$

Thus $F(\bar{s}) = \big(F_1(\bar{s}), \ldots, F_m(\bar{s})\big)$ maps the simplex $\sum_j \bar{s}_j = 1$ into itself. As $h > d_j$, we have $F_j(\bar{s}) > 0$ whenever $\bar{s}_j \geq 0$, and the closed convex set $\sum_j \bar{s}_j = 1$, $0 \leq \bar{s}_j \leq 1$ is mapped into itself by F. Hence, by the Brouwer fixed point theorem (see, e.g., Deimling (1985), pg. 17, for a proof), F has a fixed point in this set. Since $\bar{s}_j = 0$ is impossible as

$b_j > 0$, F has a fixed point with $0 < \bar{s}_j < 1$, $\sum_j \bar{s}_j = 1$. (When there is only one group, then $\bar{s}_j = \bar{s}_1 = 1$.)

To prove uniqueness, assume there are two DFE solutions $s = (s_1, \ldots, s_m)^T$ and $\bar{s} = (\bar{s}_1, \ldots, \bar{s}_m)^T$, where all s_j, $\bar{s}_j$ must be positive (as $b_j > 0$). Then, from (3.1),

$$0 = b_j + s_j \left(-d_j - b + \sum_k d_k s_k \right) = b_j + \bar{s}_j \left(-d_j - b + \sum_k d_k \bar{s}_k \right). \tag{3.6}$$

Note that the terms multiplying s_j and $\bar{s}_j$ in brackets must be negative for a steady state to exist. But (3.6) can be rewritten as

$$(-d_j - b)(s_j - \bar{s}_j) = \bar{s}_j \sum_k d_k(\bar{s}_k - s_k) + (\bar{s}_j - s_j) \sum_k d_k s_k,$$

which gives

$$(s_j - \bar{s}_j) \left(\sum_k d_k s_k - d_j - b \right) = \bar{s}_j \sum_k d_k(\bar{s}_k - s_k).$$

Assuming the right side is positive gives (by the sign statement above) $s_j < \bar{s}_j$ for all j, so $\sum_j s_j < \sum_j \bar{s}_j$. This is a contradiction as both sums must equal 1. Similarly if the right side is negative, there is a contradiction. So the right side must be zero, and since the term multiplying $(s_j - \bar{s}_j)$ on the left hand side of the above expression is negative, we must have $\bar{s}_j = s_j$ for all j, and the DFE is unique.

From (3.6) we also have

$$\sum_k d_k \bar{s}_k = d_j + b - b_j/\bar{s}_j \tag{3.7}$$

for any j, and in particular for $j = 1$. Hence

$$\bar{s}_j = \frac{\bar{s}_1 b_j}{b_1 + (d_j - d_1)\bar{s}_1}, \tag{3.8}$$

or equivalently, the two equalities in (3.3) hold.

Now, from (3.3) we see that

$$\frac{b_j}{d_j} - \bar{s}_j = \frac{\bar{s}_j}{d_j} \left(\frac{b_1}{\bar{s}_1} - d_1 \right),$$

and using the fact that the sum of the $\bar{s}_j$ is one, we get

$$\sum_j \frac{b_j}{d_j} - 1 = \left(\frac{b_1}{\bar{s}_1} - d_1 \right) \sum_j \frac{\bar{s}_j}{d_j}.$$

Thus, $b_1/\bar{s}_1 - d_1$, and hence the rest of the expressions in (3.3), have the same sign as $\sum b_j/d_j - 1$.

Using (3.8) for $\bar{s}_k$ in the equation for $\bar{s}_1$ from (3.6) gives (3.4) as an implicit equation for $\bar{s}_1$ in terms of the birth and natural death rates. This completes the proof. □

Note that a DFE with $\bar{s}_j = 0$ is possible if and only if $b_j = 0$, that is, the j^{th} subpopulation is non-reproducing, which is ruled out by our assumption. In the special case with equal natural death rates in each group, the DFE is given explicitly as $\bar{s}_j = b_j/b$.

To discuss the local asymptotic stability of the DFE, we need to introduce some notation. Let $L = (\lambda_{ij})$ be the matrix of effective contact rates, and set

$$\alpha_j(\bar{s}_j) = \gamma_j + b_j/\bar{s}_j + \epsilon_j = \gamma_j + \epsilon_j + d_j + b - \sum_k d_k \bar{s}_k > 0.$$

Then

$$B = \text{diag}(\alpha_j(\bar{s}_j)) \text{ and } C = \text{diag}(\bar{s}_j)$$

define $m \times m$ positive, diagonal matrices. The spectrum of a matrix A is the set of all eigenvalues of A and is denoted by $\sigma(A)$. We use $\rho(A)$ for the spectral radius of A, i.e., $\rho(A) = \max\{|z| : z \in \sigma(A)\}$. We now give our stability result in terms of a threshold parameter $R_0 = \rho(B^{-1}CL)$, (see Lajmanovich and Yorke (1976) for a discussion of similar criteria and Diekmann *et al.* (1990) for a more recent general discussion). We give an epidemiological interpretation of this threshold in Section 5.

Lemma 3.2 *Suppose that* $\sum_j b_j/d_j > 1$, *then the DFE as given in Lemma* 3.1 *is locally asymptotically stable (LAS) if and only if* $R_0 \equiv \rho(B^{-1}CL) < 1$.

Proof. Local stability of the DFE is investigated by linearizing (2.6)-(2.8) about the DFE $(i_j, r_j, n_j) = (0, 0, \bar{s}_j)$. Setting $i_j = \tilde{i}_j$, $r_j = \tilde{r}_j$, $n_j = \bar{s}_j + \tilde{n}_j$, gives the linearized equations for these perturbations (dropping the $\tilde{}$ from the symbols) as

$$i_j' = -i_j \left(d_j + \epsilon_j + \gamma_j + b - \sum_k d_k \bar{s}_k - \lambda_{jj} \bar{s}_j \right) + \bar{s}_j \sum_{k \neq j} \lambda_{jk} i_k, \tag{3.9}$$

$$r_j' = -r_j \left(d_j + \delta_j + \beta_j + b - d_j \bar{s}_j \right) + \gamma_j i_j + r_j \sum_{k \neq j} d_k \bar{s}_k, \tag{3.10}$$

$$\begin{aligned} n_j' = -n_j \left(d_j + b - \sum_k d_k \bar{s}_k - d_j \bar{s}_j \right) + \bar{s}_j \sum_k (\epsilon_k i_k + \delta_k r_k) \\ - \epsilon_j i_j - \delta_j r_j + \bar{s}_j \sum_{k \neq j} d_k n_k. \end{aligned} \tag{3.11}$$

We can write the matrix obtained from this system in block form

$$A = \begin{pmatrix} A_{11} & 0 & 0 \\ A_{21} & A_{22} & 0 \\ A_{31} & A_{32} & A_{33} \end{pmatrix}, \tag{3.12}$$

thus stability depends only on the $m \times m$ matrices A_{ii}, $i = 1, 2, 3$. From (3.9) and (3.7), the main diagonal terms of A_{11} are $-\alpha_j(\bar{s}_j) + \lambda_{jj}\bar{s}_j$, and $A_{11} = -B + CL$. So, if I denotes the $m \times m$ identity matrix

$$-A_{11} = B(I - B^{-1}CL) \tag{3.13}$$

has the Z-matrix sign pattern (see, e.g., Berman and Plemmons (1979), Ch. 6). Thus A_{11} is (negative) stable if and only if $I - B^{-1}CL$ is a nonsingular M-matrix, that is if and only if $R_0 \equiv \rho(B^{-1}CL) < 1$. Matrix A_{22} is diagonal with main diagonal terms equal to $-(\beta_j + \delta_j + b_j/\bar{s}_j) < 0$. Matrix A_{33} has j^{th} main diagonal term equal to $d_j\bar{s}_j - b_j/\bar{s}_j$, and (j,k) term equal to $d_k\bar{s}_j$ for $j \neq k$, thus

$$A_{33} = -\mathrm{diag}(b_j/\bar{s}_j) + (\bar{s}_1, \ldots, \bar{s}_m)^T(d_1, \ldots, d_m). \tag{3.14}$$

The matrix $(-A_{33})$ is a Z-matrix, and so is an M-matrix if and only if each leading principal minor is positive (see, e.g., Berman and Plemmons (1979), Ch. 6). Using the fact that A_{33} is a rank 1 perturbation of a diagonal matrix, we find

$$\det(-A_{33}) = \prod_{k=1}^{m}\left(\frac{b_k}{\bar{s}_k}\right)\left(1 - \sum_j \frac{d_j}{b_j}\bar{s}_j^2\right). \tag{3.15}$$

Thus each leading principal minor is positive if and only if

$$1 > \sum_j \frac{d_j}{b_j}\bar{s}_j^2. \tag{3.16}$$

But, from (3.3),

$$1 - \sum_j \frac{d_j}{b_j}\bar{s}_j^2 = \left(\frac{b_1}{\bar{s}_1} - d_1\right)\sum_j \frac{\bar{s}_j^2}{b_j},$$

so (3.16) is true if and only if $b_1 > d_1\bar{s}_1$. Since $\sum_j b_j/d_j > 1$, this holds by (3.3) in Lemma 3.1.

Combining these results, as

$$\sigma(A) = \bigcup_{i=1}^{3}\sigma(A_{ii}),$$

we obtain the local asymptotic stability characterization of our lemma. □

The principal minor method used in our proof of the stability of A_{33} has been used by several authors to derive threshold conditions in related models, see for example, May and Anderson (1984), Hethcote and Van Ark (1987) and Andreasen and Christiansen (1989).

When $\sum_j b_j/d_j > 1$, a simpler sufficient condition for LAS is given by

$$\rho\left[(\mathrm{diag}(\alpha_j(1)))^{-1}\,L\right] < 1.$$

This result is independent of $\bar{s}_j$, but is not sharp. If $R_0 > 1$ then the DFE is unstable. When $\sum_j b_j/d_j = 1$, then the linearized method is inconclusive. For the 1-group model analyzed in Busenberg and van den Driessche (1990) the spectral radius inequality becomes $\lambda < b + \gamma + \epsilon$; and the DFE, namely $(\bar{s}, \bar{i}, \bar{r}) = (1, 0, 0)$, is proved to be *globally* asymptotically stable when $\lambda \leq b + \gamma + \epsilon$. For this single group model, $\bar{s}$ is independent of the natural birth and death rates. In the special m-group case with all d_j equal, recall that $\bar{s} = b_j / \sum b_k$, hence $\bar{s}_j$ is independent of the d_j but is a monotone increasing function of b_j. It is a monotone decreasing function of each b_k for $k \neq j$. In the general m-group case, under the LAS conditions imposed by Lemma 3.2, we can determine how changes in the natural birth and death rates change the DFE values of $\bar{s}_j$.

Lemma 3.3 *Suppose that $m \geq 2$, and the d_j are not all equal. If $\bar{s}_j$, $j = 1, \ldots, m$, is the DFE value of the susceptible proportion, then*

$$\frac{\partial \bar{s}_j}{\partial d_j} < 0, \qquad \frac{\partial \bar{s}_j}{\partial b_j} > 0, \qquad \frac{\partial}{\partial d_j}\left(\sum_{k \neq j} \bar{s}_k\right) > 0, \quad \textit{and} \quad \frac{\partial}{\partial b_j}\left(\sum_{k \neq j} \bar{s}_k\right) < 0.$$

Proof. Taking partial derivatives of (3.3) with respect to d_1 for $j = 2, \ldots, m$, gives

$$\frac{\partial \bar{s}_j}{\partial d_1} = \frac{\bar{s}_j^2}{b_j}\left[1 + \frac{b_1}{\bar{s}_1^2}\frac{\partial \bar{s}_1}{\partial d_1}\right],$$

and since $\sum \bar{s}_j = 1$, we have

$$\sum_{j \neq 1} \frac{\partial \bar{s}_j}{\partial d_1} = -\frac{\partial \bar{s}_1}{\partial d_1},$$

hence

$$-\frac{\partial \bar{s}_1}{\partial d_1} = \sum_{j \neq 1} \frac{\bar{s}_j^2}{b_j}\left[1 + \frac{b_1}{\bar{s}_1^2}\frac{\partial \bar{s}_1}{\partial d_1}\right].$$

Thus

$$-\frac{\bar{s}_1^2}{b_1} < \frac{\partial \bar{s}_1}{\partial d_1} < 0 \quad \text{and} \quad 0 < \frac{\partial}{\partial d_1}\left(\sum_{j \neq 1} \bar{s}_j\right) < \frac{\bar{s}_1^2}{b_1}.$$

The proofs of the other inequalities follow in a similar way. □

By the continuity of the partial derivatives of the s_j with respect to the parameters, the inequalities of the above lemma hold for s_j close to $\bar{s}_j$. These results show that, close to the DFE, the value of s_j, for a fixed group j, decreases if the natural death rate in that group increases, and increases if the birth rate in that group increases. However, an increase in the death rate of the k-th group results in an increase in the overall equilibrium population level of the other groups. Conversely, an increase in the birth rate of the k-th group results in a decrease in the overall equilibrium population level of the other groups.

Assuming that the population has settled to the proportions given by the DFE $\bar{s}_j$ as given in Lemma 3.1, we now derive the demographic threshold condition which determines whether or not the total population remains stationary, increases, or decreases.

Lemma 3.4 *Let*

$$R_1 = \sum_j \frac{b_j}{d_j}.$$

If the subpopulation proportions have settled to the disease-free equilibrium values $(\bar{s}_j, 0, 0)$ *then as* $t \to \infty$ *the total population* $N(t) \to \infty$ *if* $R_1 > 1$, $N(t) =$*constant, if* $R_1 = 1$, *and* $N(t) \to 0$ *if* $R_1 < 1$. *In fact, if* $R_1 > 1$ *and* $R_0 < 1$, *then if the initial population proportions* $(s_j(0), i_j(0), r_j(0))$ *are feasible and sufficiently close to their equilibrium values,* $N(t) \to \infty$ *as* $t \to \infty$

Proof. When the proportions are at their steady state values, the result follows from (2.4) which gives $N' = N\left(b - \sum_j d_j \bar{s}_j\right) = N(b_1/\bar{s}_1 - d_1)$, from (3.3). Thus Lemma 3.1 shows that the total population is increasing exponentially, decreasing exponentially, or staying constant according as $R_1 = \sum_j b_j/d_j > 1$, < 1 or $= 1$.

When $R_1 > 1$ and $R_0 < 1$ the steady state proportions $(\bar{s}_j, 0, 0)$ is locally asymptotically stable by Lemma 3.2. Hence, the limiting form of Eq. (2.4) is $N' = N(b_1/\bar{s}_1 - d_1)$, and since this is a one dimensional differential equation, $N(t)$ has the same asymptotic behavior as the solutions of this limiting equation. □

We now summarize our results concerning the disease-free equilibrium. We have shown that a unique feasible disease-free equilibrium for the proportions always exists, and that there are two thresholds, R_0 and R_1. The first of these determines the stability of the disease-free state when the total population is growing, while the second determines whether or not the total population will grow, decrease or stay constant. In contrast to the case of a single population for which the complete global stability has been determined by Busenberg and van den Driessche (1990), we have only established a criterion for the local stability and instability of this unique disease-free equilibrium.

4 Endemic Proportion Equilibrium

For an endemic proportion equilibrium to exist, equations (2.5)–(2.8) with zero left hand sides must be satisfied. Recall that $n_j = s_j + i_j + r_j$ with $\sum_j n_j = 1$, so $\sum_j n_j' = 0$. If $0 \le s_j,\ i_j,\ r_j \le 1$, then from (2.5)–(2.7),

$$s_j = 0 \Rightarrow s_j' > 0,\ i_j = 0 \Rightarrow i_j' \ge 0 \text{ and } r_j = 0 \Rightarrow r_j' \ge 0.$$

Thus the flow $\pi(t)$ induced by this system maps the closed convex set

$$\mathcal{L} = \left\{ 0 \le s_j,\ i_j,\ r_j \le 1,\ \sum_j (s_j + i_j + r_j) = 1 \right\}$$

onto itself. The point $\bar{p} = \{s_j = \bar{s}_j,\ i_j = 0,\ r_j = 0\}$ is on the boundary of $\mathcal{L}$ and is a fixed point of $\pi : \pi(t)\cdot\bar{p} = \bar{p}$ for all $t \geq 0$. If the disease-free equilibrium were an extreme point of $\mathcal{L}$, we could conclude that when $R_0 > 1$, there is another fixed point of π which is in the interior of $\mathcal{L}$, that is, it is an endemic state. This does happen in the case of a single population, however, the disease-free state is in general not an extreme point of $\mathcal{L}$ when there are several subpopulations. It may be possible to adapt the results of Hofbauer (1990) on saturated fixed points in order to prove the existence of an endemic proportion equilibrium in our case also, but this has yet to be done and this problem remains open. It has recently been proved by Huang, Cooke and Castillo-Chavez (1992) that *multiple* endemic equilibria are possible in a multigroup model for HIV/AIDS transmission with total proportionate mixing and constant input of susceptibles.

5 Thresholds

In addition to the threshold parameter R_0 governing local stability of the disease free proportion equilibrium, we find other parameters are important for governing the model behavior. From (2.4) we have the equation for the total population number

$$N' = N\left[b - \sum_j \left(d_j n_j + \epsilon_j i_j + \delta_j r_j\right)\right]. \tag{5.1}$$

If an endemic equilibrium (s_j^*, i_j^*, r_j^*) exists, then defining

$$\bar{R}_1 = \frac{b}{\sum_j \left(d_j n_j^* + \epsilon_j i_j^* + \delta_j r_j^*\right)}, \tag{5.2}$$

we have the threshold result that, for initial data where the proportions tend to the endemic equilibrium, if $\bar{R}_1 < 1$, we have $N \to 0$, whereas if $\bar{R}_1 > 1$, then $N \to \infty$ as $t \to \infty$. Note that, if we substitute the DFE proportions instead of the endemic equilibrium proportions in the definition of the demographic threshold parameter $\bar{R}_1$, we obtain $b/\sum d_j \bar{s}_j$. By Lemma 3.1, this expression is greater than one if and only if the threshold parameter R_1 in Lemma 3.4 is greater than one. Thus, $\bar{R}_1$ is equivalent to the corresponding demographic threshold parameter for the case of the disease-free equilibrium when we substitute the DFE proportions in its definition instead of the endemic equilibrium proportions.

From (2.2) we have the equation for the infective number in group j when $i_j > 0$,

$$I_j' = I_j\left[-(d_j + \gamma_j + \epsilon_j) + \frac{s_j}{i_j}\sum_k \lambda_{jk} i_k\right]. \tag{5.3}$$

If an endemic equilibrium (s_j^*, i_j^*, r_j^*) is stable, then defining

$$R_2(j) \equiv \frac{s_j^* \sum_k \lambda_{jk} i_k^*}{i_j^*(d_j + \gamma_j + \epsilon_j)}, \tag{5.4}$$

we have the threshold result that if $R_2(j) < 1$ then $I_j \to 0$, whereas if $R_2(j) > 1$ then $I_j \to \infty$ as $t \to \infty$. Thus, if $\max_j R_2(j) < 1$, all $I_j \to 0$ and the disease dies out in every group, whereas if $\min_j R_2(j) > 1$ then $I_j \to \infty$ and the disease spreads in every group. If the DFE $s = \bar{s}_j > 0$ is stable, then $I_j' \geq I_j[-(d_j + \gamma_j + \epsilon_j) + s_j \lambda_{jj}]$. So in this case, we define

$$R_2(j) \equiv \frac{\bar{s}_j \lambda_{jj}}{d_j + \gamma_j + \epsilon_j}. \tag{5.5}$$

If $R_2(j) > 1$, then $I_j \to \infty$.

It is easy to see that the demographic threshold, in either one of its two forms R_1 and $\bar{R}_1$, can be viewed as the ratio of additions from births to net removals due to deaths in the total population. Similarly, the numerator of R_2 when multiplied by the total population N is the rate at which infectives are being added, while the denominator when multiplied by N is the net removal rate of infectives due to either death or recovery from the infection. Thus, R_2 is a ratio of net additions to the infective class to net removals from it. The biological interpretation of the endemic stability threshold R_0 is slightly more involved. In order to see that it has a similar interpretation as the other thresholds, we note that

$$\alpha_j = (\gamma_j + \epsilon_j + d_j) + \left(b - \sum_k d_k \bar{s}_k \right) > 0,$$

and the group of terms in the first set of parentheses is the rate of removal of infectives while the second is the net rate of addition of susceptibles to the population. Thus α_j is the rate at which the prevalence of infectives in subpopulation j is being diluted. Now, returning to the notation of Section 3, we note that the matrix $B^{-1}C$ can be written as

$$B^{-1}C = \text{diag} \left(\frac{\bar{s}_j}{\alpha_j} \right), \tag{5.6}$$

hence,

$$B^{-1}CL = \left(\frac{\lambda_{ij} \bar{s}_i}{\alpha_i} \right). \tag{5.7}$$

The entries in this matrix are ratios of the product of the susceptible fractions and the force of infection rates due to contacts between the subpopulations to the rates at which infectives are being removed from each subpopulation. Recalling that $B = \text{diag}\,(\alpha_j)$, denoting by I the $m \times m$ identity matrix, and letting $\mathbf{i}$ denote the vector with components i_j, we can rewrite the linearized equation for the i_j in the form

$$\mathbf{i}\,' = B(B^{-1}CL - I)\mathbf{i}. \tag{5.8}$$

When $R_1 = \sum(b_j/d_j) > 1$, as the entries in the diagonal matrix B are all positive, the solutions of (5.8) with positive initial data will tend to zero or infinity according as the spectral radius of $B^{-1}CL$, that is R_0, is greater or less than one. In fact, for initial data close to the disease-free equilibrium, and for small enough time intervals, we have

$$\mathbf{i}(t) = \mathbf{i}(0) + B(B^{-1}CL - I)\mathbf{i}(0)t + o(||\mathbf{i}(0)|| + t). \tag{5.9}$$

Thus, the introduction of a small proportion of infectives in a population which is at the disease-free state will result in an initial net increase of the infective when $R_0 > 1$ and in a net decrease when $R_0 < 1$. In fact, if $\mathbf{i}_0$ is proportional to the positive eigenvector of $B^{-1}CL$ whose eigenvalue is R_0, we have from (5.9)

$$i_j(t) = i_j(0) + (R_0 - 1)\alpha_j i_j(0)t + o(||\mathbf{i}(0)|| + t).$$

As suggested by a referee, R_0 is also equal to $\rho(CLB^{-1})$, this matrix CLB^{-1} describes how the next generation of infected individuals arises from the present generation.

The fine structure of the endemic thresholds that we have seen here which occurs in populations of varying size was first brought out in the work of Busenberg and van den Driessche (1990) where explicit expressions were derived for the thresholds which govern the global behavior of a single population $S \to I \to R \to S$ model. The thresholds derived here generalize those found in this single population model. In this more general case, we have not obtained the global behavior of the population when endemic conditions occur. In particular, we have not ruled out the possibility of multiple endemic states or the possible existence of oscillatory endemic solutions.

We note that, even though the model that we have treated here allows the populations to possibly grow without bound, this is not a serious limitation to the applicability of the thresholds that we have derived. In almost all communicable diseases that affect human populations, the time scale of the spread of the infection is short compared to the demographic time scales. Consequently, the factors which may eventually limit demographic growth seldom have a major influence on the thresholds that determine the course of such epidemics. However, as we have seen above, there is indeed a significant interaction between demography and epidemics since all of the basic thresholds depend on various combinations of demographic and epidemiological parameters, such as the birth and death rates and the disease transmission contact rates.

References

Anderson, R., and May, R. (1985): Age-related changes in the rate of disease transmission: implication for the designing of vaccination programs. J. Hyg. Camb. **94**, 365–436.

Anderson, R. May, R., and McLean, A. (1988): Possible demographic consequences of AIDS in developing countries. Nature **332**, 228–233.

Andreasen and Christiansen (1989): Persistence of an infectious disease in a subdivided population. Math. Biosc. **96**, 239–253.

Bernoulli, D. (1760): Essai d'une nouvelle analyze de la mortalité causée par la petite vérole et des avantages de l'inoculation pour la prévenir. Mémoire de Mathematiques et de Physique, Academie Royale des Sciences, Paris, 1–45.

Berman and Plemmons (1979): Nonnegative Matrices in the Mathematical Sciences. Academic Press, New York.

Brauer, F. (1990): Models for the spread of universally fatal diseases. J. Math. Biol. **28**, 451–462.

Brauer, F. (1991): Models for the spread of universally fatal diseases II. In: Differential Equations Models in Biology, Epidemiology and Ecology, S. Busenberg and M. Martelli (Eds.), Springer-Verlag, Berlin, Heidelberg, New York. 57–69.

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

Busenberg, S., and Cooke, K. (1982): Models of vertically transmitted diseases with sequential-continuous dynamics. In Nonlinear Phenomena in Mathematical Sciences, V. Lakshmikantham editor, Academic Press, 179–187.

Busenberg, S., and Cooke, K. (1988): The population dynamics of two vertically transmitted infections. Theor. Pop. Biol. **33**, 181–198.

Busenberg, S., Cooke, K., and Iannelli, M. (1988): Endemic thresholds and stability in a class of age-structured epidemics. SIAM J. Applied Math. **48**, 1379–1395.

Busenberg, S., Cooke, K., and Pozio, A. (1983): Analysis of a model of a vertically transmitted disease. J. Math. Biol. **17**, 305–329.

Busenberg, S., Cooke, K., and Thieme, H. (1991): Demographic change and persistence of HIV/AIDS in a heterogeneous population, SIAM J. Applied Math. **51**, 1030–1052.

Busenberg, S., and Hadeler, K. (1990): Demography and epidemics. Math. Biosc. **101**, 63–74.

Busenberg, S., and Vargas, C. (1991): Modeling Chagas' disease: variable population size and demographic implications. In Mathematical Population Dynamics, O. Arino, D. Axelrod and M. Kimmel, Editors, Marcel Dekker, New York, Basel, Hong Kong. 283–296.

Busenberg, S., and van den Driessche, P. (1990): Analysis of a disease transmission model in a population with varying size. J. Math. Biol. **28**, 257–270.

Capasso, E., and Serio, G. (1978): A generalization of the Kermack-McKendrick deterministic epidemic model. Math. Biosci. **42**, 43–61.

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

Deimling, K. (1985). Nonlinear Functional Analysis. Springer-Verlag, Berlin, Heidelberg, New York, Tokyo.

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

Gao, L., and Hethcote, H. (1992): Disease transmission models with density dependent demographics. J. Math. Biol. **30**, 717–732.

Hethcote, H. (1978): An immunization program for a heterogeneous population. Theor. Pop. Biol. **14**, 338–349.

Hethcote, H., and Thieme, H. (1985): Stability of the endemic equilibrium in epidemic models with subpopulations. Math. Biosci. **75**, 205–227.

Hethcote, H., and Van Ark, J. (1987): Epidemiological models for heterogeneous populations: proportionate mixing, parameter estimation and immunization programs. Math. Biosci. **84**, 85–118.

Hethcote, H., and Yorke, J. (1984): Gonorrhea Transmission Dynamics and Control. Lecture Notes in Biomathematics **56**, Springer-Verlag, Berlin- Heidelberg- New York.

Hofbauer, J., (1990): An index theorem for dissipative semiflows. Rocky Mountain J. of Math. **20**, 1017–1031.

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

Jacquez, J., Simon, C., Koopman, Sattenspiel, L., and Perry, T. (1988): Modelling and analyzing HIV transmission: the effect of contact patterns. Math. Biosci. **92**, 119–199.

May, R., and Anderson, R. (1984): Spatial heterogeneity and the design of immunization programs. Math. Biosc. **72**, 83–111.

McKendrick, A. (1926): Applications of mathematics to medical problems. Proc. Edin. Math. Soc. **44**, 98–130.

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

Nold, A. (1980): Heterogeneity in disease-transmission modeling. Math. Biosci. **52**, 227–240.

Pugliese, A. (1990): Population models for diseases with no recovery. J. Math. Biol. **28**, 65–82.

Sattenspiel, L. (1987): Population structure and spread of disease. Hum. Biol. **59**, 411–438.

Sattenspiel, L., and Simon, C. (1988): The spread and persistence of infectious diseases in structured populations. Math. Biosc. **90**, 341–366.

Travis, C., Post, W., and DeAngelis, D. (1980): Infectious diseases in a spatially heterogeneous environment. In, Differential Equations , Academic Press, New York. 271–278.