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REPRODUCTION NUMBERS AND THE STABILITY OF EQUILIBRIA OF SI MODELS FOR HETEROGENEOUS POPULATIONS*

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Abstract. A major project in deterministic epidemiological modeling of heterogeneous populations is to find conditions for the local and global stability of the equilibria and to work out the relations among these stability conditions, the thresholds for epidemic take-off and endemicity, and the basic reproduction number(s). Most of the work to date has been on models of homogeneous populations of constant size. Motivated by their analysis of models of the dynamics of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), the authors carry out this project for SI models of diseases that have multiple stages, which can lead to death, and which infect heterogeneous populations with intricate mixing patterns and varying sizes. In such models, it is even difficult to find the analytical expression for the stability threshold and the reproduction number. The authors show how the number of disease-transmitting contacts by infectives can be used as a Lyapunov function to carry out a systematic stability analysis in these complex models, to compute the expressions for the thresholds and reproductions numbers, and to construct a reproduction function as a cornerstone of the study of the dynamics of disease spread.

Key words. epidemiology, reproduction number, stability threshold

AMS(MOS) subject classifications. 92A15, 34D20

1. Introduction.

A major project in deterministic epidemiological modeling of heterogeneous populations is to find conditions for local and global stability of the equilibria and to work out the relations among these stability conditions, the thresholds for epidemic take-off, and endemicity, and the basic reproduction number(s). Most of the work to-date has been on models of populations with no deaths due to the disease and with birth rates equal to background death rates, resulting in population subgroups that are constant in size. Analytically, such systems prove to be fairly simple; the only nonlinear terms in the differential equations are quadratic. Nevertheless, even here, complete results on the stability of the equilibria are not yet available.

The spread of acquired immunodeficiency syndrom (AIDS) has forced us to look at models in which deaths due to the disease play a major role. The equations of such systems are more complicated than those of systems of constant population size, and the investigation of the stability of the equilibrium states is correspondingly more difficult. Anderson and May [1] and May and Anderson [2] point out the potential impact of diseases on population size and the possible demographic effects of AIDS [3]. For background on the properties of epidemiological models for homogeneous, randomly mixing populations, see Hethcote [4].

For heterogeneous populations, Lajmanovich and Yorke [5] provide a complete

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description of the dynamics of SIS systems for subpopulations of constant size. Let A denote the Jacobian matrix of the SIS system at the disease-free equilibrium and let $s(A)$ denote the maximum real part of the eigenvalues of A, the stability modulus of A. By standard theory, if $s(A) < 0$, the disease-free equilibrium is locally asymptotically stable; if $s(A) > 0$, it is unstable. Lajmanovich and Yorke [5] use one Lyapunov function to prove that, when $s(A) < 0$, the disease-free equilibrium is unique and *globally* asymptotically stable. Furthermore, they prove that, when $s(A) > 0$, a unique interior (endemic) equilibrium exists; they use another Lyapunov function to prove that this endemic equilibrium is *globally* asymptotically stable when it exists. As a result, the dynamics of SI and SIS models with heterogeneous subpopulations of constant size is fairly well understood.

The next task of epidemiological modeling is to find analogous results for SIR, SIRS, and SEIRS models that have constant subgroup sizes and proportional or other types of mixing with constant effective contact rates. A number of papers [6]–[11] have demonstrated the global stability of the disease-free equilibrium for such models when $s(A) < 0$, and the uniqueness and/or local stability of the endemic equilibrium when $s(A) > 0$. The most difficult task is the proof of the global stability of the endemic equilibrium when $s(A) > 0$. Beretta and Capasso [12] use a skew-symmetry condition on the Jacobian matrix A to provide some sufficient conditions for the global stability of the endemic equilibrium of SIR models with constant subpopulation sizes. They also present similar results [13] for a variety of models with homogeneous populations of constant size, such as SIR, SIRS, and SIS models with disease vectors, and for a homogeneous model of parasite-host spread that does not assume constant populations. Lin and So [14], working with an SIRS model of a heterogeneous population with constant subgroup sizes, show that the endemic equilibrium is globally asymptotically stable if the contact rate between subgroups is small or if the recovery rate in each subpopulation is small. Both of these situations are small perturbations of situations in which the endemic equilibrium has been known to be globally stable: no interaction between subpopulations or no immunity from the disease.

For an SI model of the spread of human immunodeficiency virus (HIV), Jacquez, et al. [15] show that there is a function $F(\lambda)$ of the parameters of the system such that, if $F(\lambda) \leq 1$, the disease-free equilibrium is the only equilibrium, but if $F(\lambda) > 1$, the disease-free equilibrium and an endemic equilibrium are the only equilibria. If there is no interaction between the subgroups, i.e., for restricted mixing [15], then for each subgroup, the disease-free equilibrium is globally asymptotically stable if $F(\lambda) \leq 1$ and unstable if $F(\lambda) > 1$. Furthermore, these thresholds prove to be the basic reproduction numbers which have played a central role in organizing thinking about stability of the disease-free equilibria in homogeneous populations [4], [16]–[20]. Lin [21] shows that for more general types of mixing—proportional and preferred mixing—the stability modulus of the Jacobian matrix at the disease-free equilibrium is $F(\lambda)-1$, where $F(\lambda)$ is the threshold obtained by Jacquez [15], and gives conditions for the local asymptotic stability of the endemic equilibrium under restricted mixing.

In this paper, we focus on the SI models with death due to the disease that have been used to study the spread of HIV. To provide background and to show how deaths due to the disease complicate the analysis, we also analyze SI models without deaths due to the disease. This comparison carries over to SIS, SIR, and SIRS models; however, we do not discuss those here. We introduce a Lyapunov function that is very useful in analyzing the stability of the disease-free equilibrium for the epidemiological models that we have looked at so far. With use of this Lyapunov function, the thresholds for stability of the disease-free equilibrium that result from

this analysis define reproduction numbers for the subgroups of the population in a very natural way.

In this analysis, we use a rather general method of specifying mixing between subgroups that we have called *structured mixing* [22]. Structured mixing easily describes a variety of mixing patterns, random and nonrandom, including restricted, proportional and preferred mixing [15], and varieties of near-neighbor and hierarchical [22]–[24] mixing patterns. This approach provides some results on the local and global stability of the disease-free and endemic equilibria, but not nearly as many as we would like. More importantly, it provides considerable insight into the effects of the interactions between the population subgroups and ties together global and local stability criteria, thresholds, and reproduction numbers.

In the SI models that we examine, we assume constant recruitment rates into the susceptible classes of each subgroup and no migration between subgroups. If there are no deaths due to the disease, there is a stable invariant set in which death rates equal birth rates, giving the types of models that have received the most attention in the literature. When there are deaths due to the disease, the problem is more difficult, but constant recruitment gives the simplest models without age structure and is not a bad assumption for spread of HIV in homosexual groups. A more realistic model would include age structure and birth and death rates dependent on age; we view that as a next stage, and a much more difficult one at that.

To maintain an even flow of ideas, we delay the presentation of some of the longer technical proofs to the appendices of this paper.

2. Models and notation. In this section we present the SI models and notation used in this paper. There is a marked difference between the nonlinear terms in the differential equations that include deaths due to the disease compared to the equations where there are no deaths due to the disease. We classify the models on that basis and on whether there are multiple stages to the infectious period. Our concern with multiple stages of infection is another outgrowth of our work [15] with models of the spread of HIV.

Figures 1(a) and 1(b) show the compartmental diagrams for SI models without and with deaths due to the disease, for the situation in which the infectious period has only one stage. Figures 2(a) and 2(b) give the corresponding models with m stages of infection. Venereal warts, caused by the human papilloma virus, and ordinary herpes are examples of sexually transmitted diseases without deaths due to the disease, although both are not quite SI diseases because of partial immunity. AIDS is the example of an SI disease with death due to the disease. Although our main focus is on the latter, we present results on SI models without deaths due to the disease because the simplification in the dynamics of such models throws light on the case with disease-related deaths.

2.1. Notation. In these models, X_i is the number of susceptibles in subpopulation i, and Y_{ir} is the number in subpopulation i who are in stage r of infection for $r = 1, \cdots, m$. Other symbols used have the following definitions.

U_i denotes a constant recruitment rate of susceptibles into subgroup i, in units persons/time.

μ denotes the fractional death rate from competing causes. This is the fraction removed per unit time by all competing causes, assumed to be constant and the same for all susceptibles and infecteds.

k denotes the fractional rate of transfer of infecteds from one stage to the next and out of the final stage. For one stage, k is the fractional death rate due to the

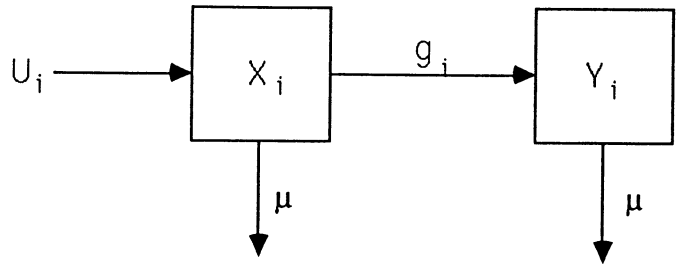

FIG. 1(a). SI *model for subgroup i, without death due to the disease.*

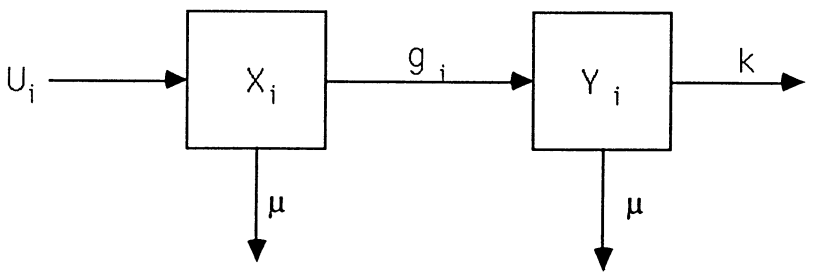

FIG. 1(b). SI *model with death due to the disease.*

disease. For multiple stages, it is the fractional death rate as well as the transfer rate between stages of infection. For HIV, transfer from the last stage of infection leads to full-blown AIDS, in which the infected person is so ill he no longer takes part in the transmission process, so it is death as far as the transmission system is concerned. We note that the structure of the stages can be generalized by allowing the transfer rate constants between the stages to differ. However, that is not done here. Note that the case of the same k for all transfers gives a gamma function for the density function of incubation times to AIDS, a hypothesis that fits the data available so far.

c_i denotes the mean number of persons contacted (partners) per person in subgroup i, per unit time.

β_{jr} denotes the probability of catching the disease given a contact with an infected in subgroup j who is in stage r.

g_i denotes the fraction of susceptibles in subgroup i that become infected per unit time: g_i is a function of the number of susceptibles and infecteds in all subgroups, the contact rates between susceptibles and infecteds, and the parameters c_i and β_{jr}. In particular, g_i depends on the ways in which the subgroups mix. It has the following properties:

(1) g_i is an increasing function of Y_i and a decreasing function of X_i.
(2) If g_i is a function of Y_j, $j \neq i$, it increases monotonically in Y_j.
(3) If g_i is a function of X_j, $j \neq i$, it decreases monotonically in X_j.
(4) Each $g_i = 0$ when $\mathbf{Y} = \mathbf{0}$.

2.2. Equations. In this section we write the equations for these systems in

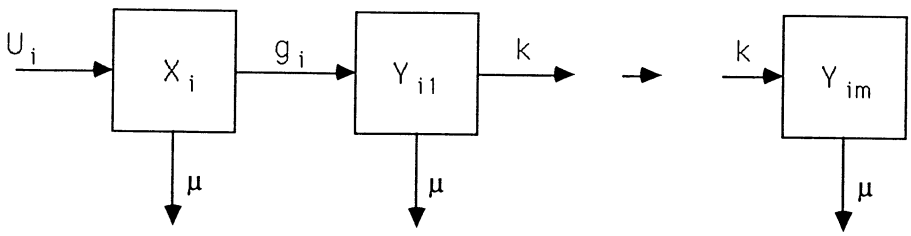

FIG. 2(a). SI *model without deaths due to the disease with m stages of infection.*

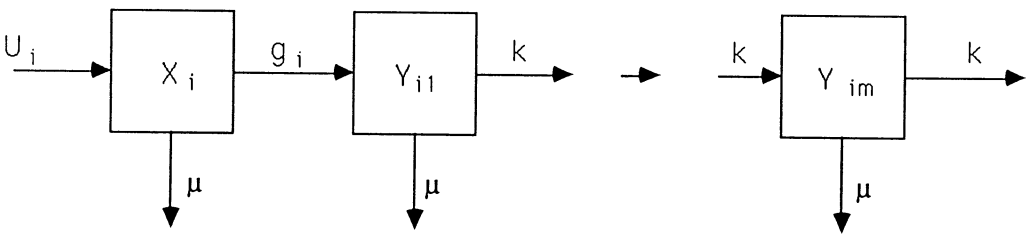

FIG. 2(b). SI *model with deaths due to the disease, with m stages of infection.*

general form.

2.2.1. No deaths due to the disease. The equations for the system follow directly from the definitions and the compartmental diagrams. For one infected stage with no disease-related deaths, the equations are

$$\dot{X}_i = -X_i g_i - \mu X_i + U_i, \tag{1}$$

$$\dot{Y}_i = X_i g_i - \mu Y_i. \tag{2}$$

If there are multiple stages to the infection, (2) is replaced by (3)–(5) as follows:

$$\dot{Y}_{i1} = X_i g_i - (k+\mu) Y_{i1}, \tag{3}$$

$$\dot{Y}_{ir} = k Y_{i,r-1} - (k+\mu) Y_{ir}, \qquad r = 2, \cdots, m-1 \tag{4}$$

$$\dot{Y}_{im} = k Y_{i,m-1} - \mu Y_{im}. \tag{5}$$

Examination of these equations reveals an important simplifying property of the equations without deaths due to the disease. Adding (1) and (2), or (1), (3), (4) for $r = 2, \cdots, m-1$, and (5) gives $\dot{N}_i = U_i - \mu N_i$, where $N_i = X_i + \sum_{r=1}^{m} Y_{ir}$ is the total population in subgroup i. Since the general solution of $\dot{N}_i = U_i - \mu N_i$ is

$$N_i(t) = \kappa e^{-\mu t} + U_i/\mu,$$

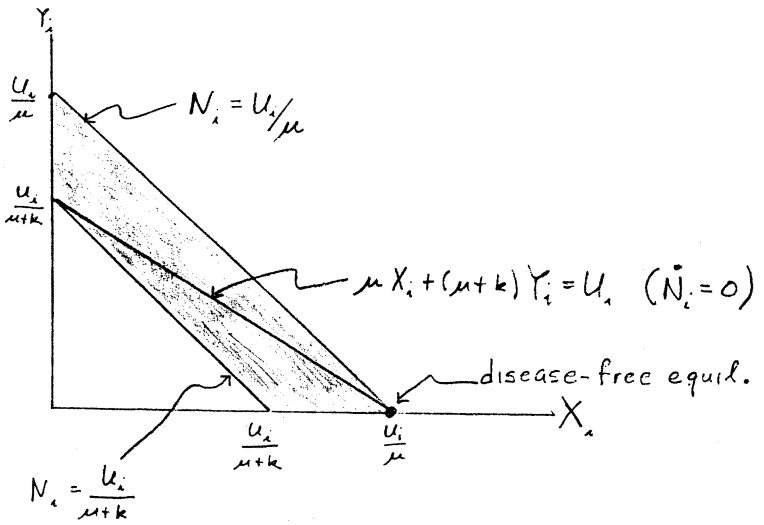

FIG. 3

$N_i = U_i/\mu$ is an asymptotically stable, invariant hyperplane, and we need only study the dynamics restricted to this hyperplane.

On this invariant hyperplane, the constant μ is both the birth-rate constant and the death-rate constant, and the population size N_i is constant. The latter property allows us to change the equations to equations in the *fractions* of the population that are susceptible and infected by dividing (1)–(5) by N_i, a process that usually simplifies the expression for g_i. SIS, SIR, and SIRS models without deaths due to the disease have the same property. A major part of the pre-AIDS modeling was concerned with such systems.

2.2.2. Deaths due to the disease. In models with deaths due to the disease, (1), (3), and (4) remain the same; only (2) and (5) change. For comparison, we write the full set of equations (1a)–(5a) as follows

$$\dot{X}_i = -X_i g_i - \mu X_i + U_i, \tag{1a}$$

$$\dot{Y}_i = X_i g_i - (k+\mu) Y_i, \tag{2a}$$

$$\dot{Y}_{i1} = X_i g_i - (k+\mu) Y_{i1}, \tag{3a}$$

$$\dot{Y}_{ir} = k Y_{i,r-1} - (k+\mu) Y_{ir}, \qquad r = 2, \cdots, m-1 \tag{4a}$$

$$\dot{Y}_{im} = k Y_{i,m-1} - (k+\mu) Y_{im}. \tag{5a}$$

One infectious stage. Adding (1a) and (2a) for one stage of infection gives

$$\dot{N}_i = U_i - \mu N_i - k Y_i \quad \text{or} \quad \dot{N}_i = U_i - (k+\mu) N_i + k X_i.$$

Since $\dot{N}_i < 0$ when $U_i - \mu N_i < 0$, and $\dot{N}_i > 0$ when $U_i - (\mu + k) N_i > 0$, the region between the hyperplanes $N_i = U_i/\mu$ and $N_i = U_i/(\mu + k)$ is a globally attractive, invariant region. In addition, all equilibria fall on the subspace $(k+\mu) Y_i + \mu X_i = U_i$ for all i, where $\dot{N}_i = 0$. These hyperplanes are drawn in X_i–Y_i space in Fig. 3, where the invariant region is shaded in.

Multiple infectious stages. Adding (1a), and (3a)–(5a) for multiple infectious stages, shows similarly that the region between $N_i = U_i/\mu$ and $N_i = U_i/(k + \mu)$ for

all i, is an invariant region. Now, however, all equilibria fall on the subspace,

$$\frac{U_i}{\mu} = X_i + \frac{1}{1-(k/(k+\mu))^m} Y_i, \qquad i = 1, \cdots, n.$$

2.2.3. Summary. The following proposition summarizes the observations of this section.

PROPOSITION 1. (i) *For* (1)–(5) *with no disease-related deaths, the affine subspace* $N_i = U_i/\mu_i$, $i = 1, \cdots, n$ *is a globally, asymptotically stable, invariant subspace.*

(ii) *For* (1a)–(5a) *with disease-related deaths, the region described by*

$$\frac{U_i}{\mu + k} \le N_i(t) \le \frac{U_i}{\mu}, \qquad i = 1, \cdots, n \tag{6}$$

is a globally, asymptotically stable, invariant region. Furthermore, all equilibria lie on the affine subspace

$$\mu X_i + \frac{\mu}{1-(k/(k+\mu))^m} Y_i = U_i, \qquad i = 1, \cdots, n.$$

For the one-stage case, this expression simplifies to

$$\mu X_i + (\mu + k) Y_i = U_i, \qquad i = 1, \cdots, n.$$

3. Structured mixing. The fractional transfer rate from susceptibles to infectives g_i depends on how the subgroups mix with one another. In this paper, we use a type of mixing called structured mixing, which is general enough to include a large variety of mixing patterns, including the ones commonly used in the literature, such as restricted mixing and proportional mixing.

Structured mixing [22] was defined to model the spread of a sexually transmitted disease in which sexual contacts are made in a number of different social and geographic settings. For this purpose, we define M *activity groups*, which are the interacting groups in the different settings where contacts are made. The allocation of contacts to different activity groups is given by the entries of an $n \times M$ matrix $\mathbf{f}$; f_{is} gives the fraction of population subgroup i's contacts that are made in activity group s. Note that M may be greater than, equal to, or less than n. The only constraint on $\mathbf{f}$ is that $\sum_s f_{is} = 1$. However, the mixing within each activity group is subject to the symmetry constraint for sexual contacts, namely, the number of contacts of i with j in s must equal the number of contacts of j with i in s.

A large variety of mixing patterns are special cases of structured mixing that include restricted, proportional, and preferred mixing [15]. In restricted mixing, people make contacts only with members of the same group. That is easily specified in structured mixing terms by setting $M = n$ and $f_{is} = \delta_{is}$, where δ_{is} is the Kronecker delta. In the literature, in what is commonly called proportional mixing, individuals make contacts at random. In that case, the fraction of population subgroup i's contacts that are with population subgroup j, ρ_{ij} is simply the fraction of the total contacts made by subgroup j:

$$\rho_{ij} = \frac{c_j N_j}{\sum_p c_p N_p}.$$

In structured mixing terms, $M = 1$, $f_{i1} = 1$ for all i, and ρ_{ij} gives the fraction of group i's contacts that are with group j. In preferred mixing, a fraction r_i of group i's

contacts are reserved for within-group contacts, and the fraction $(1 - r_i)$ is subject to proportional mixing. In structured mixing terms, $M = n+1$, $f_{ii} = r_i$, $f_{i,n+1} = 1 - r_i$, $f_{is} = 0$, for $s \neq i$ and for $s \neq n+1$ and mixing in the $(n+1)$th activity group is proportional mixing. Sattenspiel [23] developed a model for mixing of n geographically separate subgroups for modeling the spread of Hepatitis A. A fraction of each of the subgroups travels to social facilities associated with each subgroup, where random mixing takes place. Thus there is mixing within each subgroup and also in the social facility associated with each subgroup. This type of mixing can be described as a type of structured mixing with $M = 2n$. In addition, structured mixing can describe near–neighbor mixings of various kinds [22], hierarchical mixing patterns such as that used by Andreasen and Christiansen [24], and a variety of other nonrandom mixing patterns.

Even if the contacts within activity groups are random, so as to give proportional mixing between population subgroups within activity groups, structured mixing can give a nonrandom mixing of the population as a whole because of the nonrandom assignment of contacts to the activity groups.

3.1. The SI model with structured mixing. In this subsection we write the equations for the SI model with structured mixing, with one infected stage and with deaths due to the disease. The equations for multiple infected stages follow easily, as do those for SI models without death due to the disease. Recall that f_{is} gives the fraction of population subgroup i's contacts that are made in activity group s. The total contact rate of susceptibles from population subgroup i in activity group s must be $c_i X_i f_{is}$. Let $\rho_{ij}(s)$ be the fraction of the contacts of group i that are with members of group j, within activity group s. Assuming random allocation of the susceptibles and infecteds from each population subgroup to the activity groups, the fraction infected in group j in activity group s must be Y_j/N_j, giving

$$c_i X_i f_{is} \rho_{ij}(s) \beta_j \frac{Y_j}{N_j}$$

for the rate at which susceptibles in i are infected by contacts with infecteds from j in activity group s. Thus, in this case, g_i is given by

$$g_i = c_i \sum_s f_{is} \sum_j \rho_{ij}(s) \beta_j \frac{Y_j}{N_j}, \tag{7}$$

and (1a) and (1b) become

$$\dot{X}_i = -c_i X_i \sum_s f_{is} \sum_j \rho_{ij}(s) \beta_j \frac{Y_j}{N_j} - \mu X_i + U_i, \tag{8}$$

$$\dot{Y}_i = c_i X_i \sum_s f_{is} \sum_j \rho_{ij}(s) \beta_j \frac{Y_j}{N_j} - (\mu + k) Y_i. \tag{9}$$

3.2. Structured mixing with proportional mixing within activity groups. If the mixing within activity groups is proportional mixing, then $\rho_{ij}(s)$ is given by (10):

$$\rho_{ij}(s) = \frac{f_{js} c_j N_j}{\sum_p f_{ps} c_p N_p}, \tag{10}$$

and (8) and (9) become (11) and (12):

$$\dot{X}_i = -c_i X_i \sum_s f_{is} \frac{\sum_j f_{js} c_j \beta_j Y_j}{\sum_j f_{js} c_j N_j} - \mu X_i + U_i \tag{11}$$

$$\dot{Y}_i = c_i X_i \sum_s f_{is} \frac{\sum_j f_{js} c_j \beta_j Y_j}{\sum_j f_{js} c_j N_j} - (k+\mu) Y_i. \tag{12}$$

Expressions (11) and (12) show an important consequence of death due to the disease. If there are no deaths due to the disease, N_j is constant on the asymptotically stable invariant subspace $U_j = \mu N_j$ for all j, and the first term, the nonlinear term, in (11) and (12) is a sum of *quadratic* terms. If there are deaths due to the disease, N_j is no longer constant and the first term is a sum of rational expressions, each homogeneous of degree one. This observation extends to SIS, SIR, and SIRS models.

4. A Lyapunov function for epidemiologic models. It has been our experience that *the total number of infectious contacts of the infecteds over the period of infectivity* forms a general Lyapunov function [25], [26] for epidemiological models. To motivate that choice, we point out that the disease must be spreading if the total number of infectious contacts is increasing and conversely. In this section, we will present the exact expression for this function and compute its derivative along trajectories for the cases under consideration.

4.1. One stage of infection. If there is only one stage to the infectious period, this Lyapunov function is

$$V = \sum_i \beta_i c_i D Y_i, \tag{13}$$

where D is the mean duration of the infectious period. If there are no deaths due to the disease, $D = 1/\mu$; with deaths due to the disease, $D = 1/(k+\mu)$. Thus the derivative $\dot{V}$ of V along solutions of (1,2) is

$$\begin{aligned} \dot{V} &= \frac{d}{dt} V(X(t), Y(t)) = \sum_i \left(\frac{\partial V}{\partial X_i} \dot{X}_i + \frac{\partial V}{\partial Y_i} \dot{Y}_i \right) \\ &= D \sum_i \beta_i c_i X_i g_i - \sum_i \beta_i c_i Y_i. \end{aligned} \tag{14}$$

For structured mixing with proportional mixing within activity groups, $\dot{V}$ becomes, according to (10), (12),

$$\dot{V} = D \sum_i \beta_i c_i^2 X_i \sum_s f_{is} \frac{\sum_j f_{js} c_j \beta_j Y_j}{\sum_j f_{js} c_j N_j} - \sum_i \beta_i c_i Y_i. \tag{15}$$

4.2. Multiple stages of infection. To calculate V and $\dot{V}$ for multiple infectious stages, we first need to calculate the mean duration of the infected state and the mean infectivity.

4.2.1. No deaths due to the disease: calculation of D and $\bar{\beta}$. Suppose first that there are no deaths due to the disease. Consider any cohort entering the first stage of infection. The mean sojourn time for each of the stages $1, \cdots, m-1$ is $1/(k+\mu)$, but for the mth stage it is $1/\mu$. However, of those entering stage r, only $k/(k+\mu)$ pass on to stage $r+1$. Thus the mean sojourn time in infected stages must be

$$D = \frac{1}{k+\mu}\sum_{r=1}^{m-1}\left(\frac{k}{k+\mu}\right)^{r-1} + \frac{1}{\mu}\left(\frac{k}{k+\mu}\right)^{m-1} = \frac{1}{\mu}. \tag{16}$$

Given (16), what is the mean infectivity of a cohort of size S in subgroup i that enters stage 1 of the disease? The number of infectious contacts during stage 1 must be

$$c_i S\beta_{i1}/(k+\mu).$$

Of those entering stage r, only $k/(k+\mu)$ go on to stage $r+1$. Thus the total number of infectious contacts of this cohort for all stages must be

$$I = c_i S\left[\frac{1}{k+\mu}\sum_{r=1}^{m-1}\beta_{ir}\left(\frac{k}{k+\mu}\right)^{r-1} + \frac{1}{\mu}\beta_{im}\left(\frac{k}{k+\mu}\right)^{m-1}\right]. \tag{17}$$

If we define the mean infectivity for subgroup i by

$$\bar{\beta}_i = \frac{\frac{1}{k+\mu}\sum_{r=1}^{m-1}\beta_{ir}\left(\frac{k}{k+\mu}\right)^{r-1} + \frac{1}{\mu}\beta_{im}\left(\frac{k}{k+\mu}\right)^{m-1}}{1/\mu}, \tag{18}$$

the number of infective contacts of the cohort of size S passing through all infectious stages can be written as

$$I = c_i S D\bar{\beta}_i. \tag{19}$$

4.2.2. Deaths due to the disease: calculation of D and $\bar{\beta}$. With deaths due to the disease, the mean sojourn time in infected stages becomes

$$\hat{D} = \frac{1}{k+\mu}\sum_{r=1}^{m}\left(\frac{k}{k+\mu}\right)^{r-1} = \frac{1-(k/(k+\mu))^m}{\mu}, \tag{20}$$

and the mean infectivity becomes

$$\bar{\beta}_i = \frac{\frac{1}{k+\mu}\sum_{r=1}^{m}\beta_{ir}\left(\frac{k}{k+\mu}\right)^{r-1}}{\frac{1}{k+\mu}\sum_{r=1}^{m}\left(\frac{k}{k+\mu}\right)^{r-1}}. \tag{21}$$

4.2.3. Remarks on notation. We have seen that the mean duration of the infectious period depends upon whether there are disease-related deaths and whether the disease passes through multiple stages. If there are disease-related deaths and only one stage to the infection, then this mean duration is $1/(\mu+k)$. If there are disease-related deaths and multiple stages of infection, the mean duration of the infectious

period is given by expression (20). If there are no disease-related deaths, this mean duration is $1/\mu$, regardless of whether there are multiple stages. Note that these expressions are consistent with each other. For example, if we let $k = 0$ in (20), we obtain $1/\mu$; if we let $m = 1$ in (20), we obtain $1/(k+\mu)$. We will continue to denote the mean duration of the infectious period by the letter D; the exact analytical expression for D should be clear from the particular model under consideration. When we want to emphasize that we are using expression (20) for D, we will denote expression (20) by $\hat{D}$. When we want to emphasize that we are using $1/\mu$ for D in a model with no disease-related deaths, we will denote $1/\mu$ by D_o.

Even for diseases with multiple stages of infection, $1/(k+\mu)$ is the mean duration of one stage. We will use the symbol D_1 to denote $1/(k+\mu)$, even when we are working with diseases with multiple stages.

Define b_{i1} by

$$b_{i1} = \sum_{p=1}^{m} \beta_{ip} \left(\frac{k}{\mu + k} \right)^{p-1}. \tag{22}$$

In the case of multiple stages, we use definitions (20) and (21) of $\hat{D}$ and $\bar{\beta}_i$ to compute

$$\hat{D}\bar{\beta}_i = \hat{D} \cdot \frac{D_1 b_{i1}}{\hat{D}} = D_1 b_{i1}.$$

We will often use the simpler mathematical expressions D_1 and b_{i1} in the proofs of our results for diseases with deaths and multiple stages, but we will replace $D_1 b_{i1}$ by the more natural biological expression $\hat{D}\bar{\beta}_i$ in the statements of the theorems.

4.3. The Lyapunov function for multiple stages.

4.3.1. Deaths due to the disease. For the case of multiple stages, we first derive V and $\dot{V}$ in detail for SI with deaths due to the disease and then state the results for SI without deaths due to the disease. Consider Y_{ir} persons entering the rth stage of the disease in subpopulation i. They have $c_i \beta_{ir} Y_{ir}/(k+\mu)$ infectious contacts in stage r, $c_i \beta_{i,r+1}[kY_{ir}/(k+\mu)]/(k+\mu)$ in stage $r+1$, and so on, giving us

$$\frac{1}{k+\mu} \sum_{p=r}^{m} c_i \beta_{ip} \left(\frac{k}{k+\mu} \right)^{p-r} Y_{ir}$$

for the number of infectious contacts of the Y_{ir} who entered stage r. Summing this expression over subgroups i and stages r yields the Lyapunov function (23) for the model with stages in the infectious period

$$V = \frac{1}{k+\mu} \sum_{i} c_i \sum_{r=1}^{m} \sum_{p=r}^{m} \beta_{ip} \left(\frac{k}{k+\mu} \right)^{p-r} Y_{ir}. \tag{23}$$

If we define

$$b_{ir} \equiv \sum_{p=r}^{m} \beta_{ip} \left(\frac{k}{k+\mu} \right)^{p-r}, \tag{24}$$

then we can write V in (23) as

$$V = \sum_{i,r} D_1 c_i b_{ir} Y_{ir}. \tag{25}$$

Observe that if we let $r = 1$ in expression (24) of b_{ir}, we obtain expression (22) for b_{i1}.

The derivative $\dot{V}$ of V along orbits is then

$$\dot{V} = \frac{1}{k+\mu} \sum_i c_i \sum_{r=1}^{m} \sum_{p=r}^{m} \beta_{ip} \Big(\frac{k}{k+\mu} \Big)^{p-r} \dot{Y}_{ir}. \tag{26}$$

Substituting (1a), (3a)–(5a) and canceling terms reduces (26) to

$$\dot{V} = \frac{1}{k+\mu} \sum_i c_i \Big\{ \sum_{r=1}^{m} \beta_{ir} \Big(\frac{k}{k+\mu} \Big)^{r-1} X_i g_i - (k+\mu) \sum_{r=1}^{m} \beta_{ir} Y_{ir} \Big\} \tag{27}$$

We use (21) and (24) to convert (27) to

$$\begin{aligned} \dot{V} &= \sum_i c_i \Big(\bar{\beta}_i \hat{D} X_i g_i - \sum_{r=1}^{m} \beta_{ir} Y_{ir} \Big) \\ &= \sum_i c_i (b_{i1} D_1 X_i g_i - \sum_{r=1}^{m} \beta_{ir} Y_{ir}) \end{aligned} \tag{28}$$

where the mixing that our model uses determines the g_i's.

If we use structured mixing with proportional mixing in activity groups, g_i is given by

$$g_i = c_i \sum_s f_{is} \Big(\frac{\sum_j f_{js} c_j \sum_r \beta_{jr} Y_{jr}}{\sum_j f_{js} c_j N_j} \Big). \tag{29}$$

Substituting into (28) and rearranging gives the following expression for $\dot{V}$:

$$\dot{V} = \sum_i \Big(\sum_s f_{is} \Big(\frac{\hat{D} \sum_j c_j^2 \bar{\beta}_j f_{js} X_j}{\sum_j c_j f_{js} N_j} \Big) - 1 \Big) \sum_r c_i \beta_{ir} Y_{ir} \tag{30}$$

4.3.2. No deaths due to the disease. If there are no deaths due to the disease, (27) becomes

$$\dot{V} = \sum_i c_i \Big[\sum_{r=1}^{m-1} \Big(\frac{\beta_{ir}}{(k+\mu)} \Big(\frac{k}{k+\mu} \Big)^{r-1} + \frac{\beta_{im}}{\mu} \Big(\frac{k}{k+\mu} \Big)^{m-1} \Big) X_i g_i - \sum_{r=1}^{m} \beta_{ir} Y_{ir} \Big]; \tag{31}$$

using (16) and the definition (18) of $\bar{\beta}_i$, we compute

$$\dot{V} = \sum_i c_i \Big(\bar{\beta}_i D_o X_i g_i - \sum_{r=1}^{m} \beta_{ir} Y_{ir} \Big), \tag{32}$$

which is the same as (28). The expression for $\dot{V}$ for structured mixing with proportional mixing within activity groups is the same as (30), with the appropriate change in D and $\bar{\beta}_i$.

5. The Lyapunov function, reproduction functions and reproduction numbers. In this section we begin the process of relating the functions V and $\dot{V}$ that we have constructed to the threshold and the reproduction number of an SI model.

5.1. One stage of infection. We first work with models with one stage of infection. Expression (15) for $\dot{V}$ can be rearranged in the form

$$\dot{V} = \sum_i \Big[\sum_s f_{is} \Big(\frac{\sum_j c_j^2 \beta_j D f_{js} X_j}{\sum_j c_j f_{js} N_j} \Big) - 1 \Big] c_i \beta_i Y_i. \tag{33}$$

The first term in the parentheses in (33) we call the *reproduction function*:

$$\mathcal{R}_i \equiv \sum_s f_{is} \Big(\frac{\sum_j c_j^2 \beta_j D f_{js} X_j}{\sum_j c_j f_{js} N_j} \Big). \tag{34}$$

If we write $V_i \equiv c_i \beta_i D Y_i$ for the total number of infectious contacts over the period of infectivity by persons in subgroup i, then $\dot{V}$ in (33) can be written:

$$\dot{V} = \sum_i [\mathcal{R}_i - 1] \frac{V_i}{D}. \tag{35}$$

We call $\mathcal{R}_i$ a reproduction function because it gives a mean reproduction number at any point $(X_1, \cdots, Y_n)$; when evaluated at the disease-free equilibrium $X_i = U_i/\mu, Y_i = 0$, for all i, it becomes a mean *basic* reproduction number. Some epidemiologists call $\mathcal{R}_i$ the reproduction number. However, we find it more consistent to use the term "reproduction function" for an expression that depends on the values of the X_i's and Y_i's and to use the term "reproduction number" for the reproduction function evaluated at the disease-free equilibrium. Recall that the *basic reproduction number* for a disease in a homogeneous population is $R_o = c\beta D$, where D is the mean duration of infectivity; it can be interpreted as the average number of infections due to a single infected in a population of susceptibles. If we evaluate the reproduction function $\mathcal{R}_i$ in (34) at the disease-free equilibrium $X_j = U_j/\mu$, for all j, we obtain the reproduction number

$$\mathcal{R}_{oi} = \sum_s f_{is} \left(\frac{\sum_j (c_j \beta_j D)(c_j f_{js} U_j)}{\sum_j c_j f_{js} U_j} \right). \tag{36a}$$

The ratio in the parentheses is a weighted average of the $(c_j \beta_j D)$ in activity group s, the weights being the total contact rates of population subgroups j, $j = 1, \cdots, n$, in s, for the disease-free state. Thus (36a) can also be written as

$$\mathcal{R}_{oi} = \sum_s f_{is} \langle c\beta D \rangle_s, \tag{36b}$$

showing that $\mathcal{R}_{oi}$ is a weighted average over activity groups of the mean reproduction numbers $\langle c\beta D \rangle_s$ within activity groups. We refer to $\mathcal{R}_{oi}$ as the mean basic reproduction number.

5.2. Multiple stages of infection. For multiple stages of infection, V is given by expression (23) and $\dot{V}$ by (30), which, with the proper D and $\bar{\beta}$, holds for the SI models with and without disease-related deaths. Note that (30) has the structure

$$\dot{V} = \sum_i [\mathcal{R}_i - 1] V_i^*, \tag{37}$$

which is similar to equation (35) for $m = 1$. The difference is that V_i^* is not the same as V_i/D. However, V_i^* has the same properties as V_i in that it is a positive linear function of the Y_{ir}'s. The expression for the reproduction functions $\mathcal{R}_i$ is still (34), with $\bar{\beta}_j$ from (21) replacing β_j. At the disease-free equilibrium, $\mathcal{R}_i$ becomes the mean basic reproduction number $\mathcal{R}_{oi}$, as given in expression (36a).

5.3. Strategies for analyzing the disease-free equilibria. As motivation for the usefulness of equations like (33) and (37), let us look at the simple SI model with one stage in a homogeneous population, i.e., $n = 1$, and contacts are at random. The expressions

$$\begin{aligned} \dot{X} &= -gX - \mu X + U, \\ \dot{Y} &= +gX - (\mu + k)Y, \end{aligned} \tag{38}$$

hold, where $g = c\beta Y/N$. Since $V = c\beta DY$,

$$\dot{V} = c\beta D\dot{Y} = (\mathcal{R} - 1)V^*, \tag{39}$$

where

$$\mathcal{R} = \frac{\beta cDX}{N} \quad \text{and} \quad V^* = \frac{V}{D} = c\beta Y. \tag{40}$$

At the disease-free equilibrium $(U/\mu, 0)$, $\mathcal{R}$ becomes $R_o = c\beta D$, the classical basic reproduction number.

To see that V is truly a Lyapunov function for system (38), note that the line $\{Y = 0\}$ is a global minimum of V. On this line, the dynamics (38) becomes $\dot{X} = U - \mu X$ and all orbits of (38) that start on this line stay on this line and tend to the disease-free equilibrium $X = U/\mu$. By the classical Lyapunov theorem [5], [25], [26],

(i) if $\dot{V} > 0$ in the intersection of $\{Y > 0\}$ with a ball about $(U/\mu, 0)$, then $(U/\mu, 0)$ is unstable;

(ii) if $\dot{V} < 0$ in the intersection of $\{Y > 0\}$ with a ball about $(U/\mu, 0)$, then $(U/\mu, 0)$ is locally asymptotically stable;

(iii) if $\dot{V} < 0$ throughout the interior of the stable invariant region

$$B \equiv \{(X, Y) : X \geq 0,\ Y \geq 0,\ U/(\mu + k) \leq X + Y \leq U/\mu\},$$

then $(U/\mu, 0)$ is *globally* asymptotically stable.

Since the reproduction function $\mathcal{R}$ in (40) is an increasing function of X $(\partial\mathcal{R}/\partial X > 0)$ and a decreasing function of Y $(\partial\mathcal{R}/\partial Y < 0)$, it takes its maximum value in the invariant region B at the bottom right corner $(U/\mu, 0)$. Therefore, if $R_o = \mathcal{R}(U/\mu, 0) < 1$, then $\mathcal{R} - 1$ is negative throughout B; and by (39), $\dot{V} < 0$ throughout the interior of B. So, $(U/\mu, 0)$ is a *globally* asymptotically stable equilibrium. If $R_o > 1$, then by (39), $\dot{V} > 0$ on a neighborhood of $(U/\mu, 0)$ in the interior of B, and $(U/\mu, 0)$ is an unstable equilibrium.

Let us examine this latter "$R_o > 1$" case more carefully. The level sets of $\mathcal{R}(X, Y)$ in (40) are rays from the origin. Since $\mathcal{R} - 1$ is negative on the positive Y-axis and positive on the positive X-axis, the zero set of $\mathcal{R} - 1$ must be a ray in the interior of B. This ray intersects the line $\mu X + (\mu + k)Y = U$ (which, by Proposition 1, contains all the equilibria) in a single point, as pictured in Fig. 4. Since any equilibrium of (38)

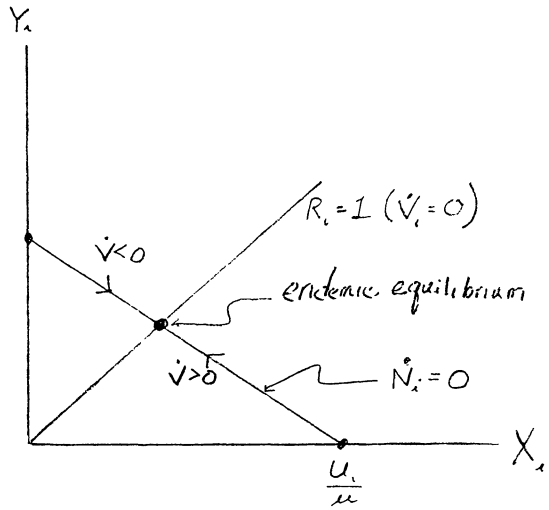

FIG. 4

in the interior of B must satisfy $\dot{V} = 0$ and therefore $\mathcal{R} - 1 = 0$ by (39), there is a unique endemic equilibrium of (38) when $R_o > 1$.

Furthermore, in the case of no disease-related deaths, we need only consider the stable invariant line $X + Y = U/\mu$. The reproduction function $\mathcal{R}$ is monotonically increasing in X. If $R_o > 1$, $\mathcal{R}$ equals 1 if and only if $X^* = U/(\mu\beta cD)$. To the left of X^*, $\dot{V} < 0$, so Y is decreasing and the dynamics flows down and to the right on the line $X + Y = U/\mu$. To the right of X^*, $\dot{V} > 0$ and the dynamics flows up and to the left on $X + Y = U/\mu$, as in Fig. 4. So, the endemic equilibrium is globally stable in the interior of B, when it exists. The analysis with use of this Lyapunov function for the disease-free equilibrium gives proof of global stability of the endemic equilibrium as a bonus, although it is a nonstandard use of the Lyapunov function.

We have to work a little harder to prove the global stability of the unique endemic equilibrium (X^*, Y^*) of (38) for the case of disease-related deaths. Figure 5 illustrates the construction of a parallelogram

$$\{(X,Y) : |N - N(X^*,Y^*)| \le b_1,\ |Y - Y^*| \le b_2\}$$

of arbitrary size about (X^*, Y^*) with V (that is, Y) and N constant on alternating sides, so that the vectors of (38) point into each of these parallelograms on their boundaries. This construction only works if the $\dot{N} = 0$ line is not too flat, i.e., if $\mu/(k + \mu)$ is not too small. We will not present the proof here but will present the proof of a more general result in the proofs of Theorems 2 and 3. We summarize the results of this section by the following well-known theorem. See, for example, Jacquez et al. [15].

THEOREM 1. *Consider the simple* SI *model* (38) *of a homogeneous population without multiple stages of infection. Let* $\mathcal{R} = c\beta DX/N$ *and* $R_o = c\beta D$. *Let* $V = c\beta DY$. *Then,* $\dot{V} = (\mathcal{R} - 1)V/D$. *If* $R_o < 1$, *the disease-free equilibrium, is the only equilibrium and it is globally asymptotically stable, with* V *a global Lyapunov function. If* $R_o > 1$, *a unique interior equilibrium arises; it is globally asymptotically stable, and the disease-free equilibrium is unstable.*

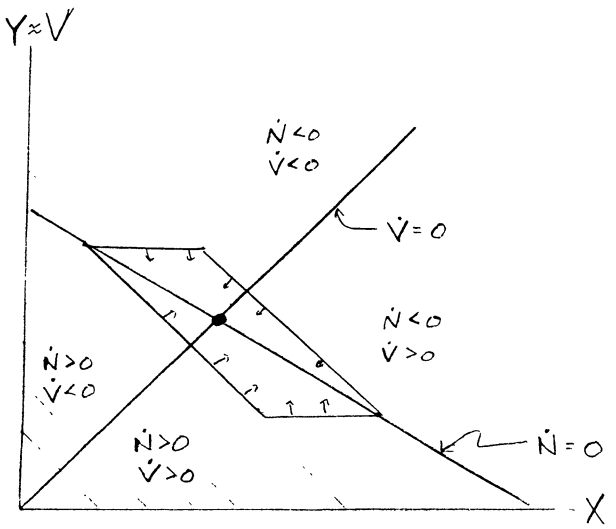

FIG. 5

This analysis of system (38) works for more general functions g of infection fraction than $g(X,Y) = c\beta Y/(X+Y)$. Our analysis requires only that

(i) $g = 0$ when $Y = 0$, so that we can write $g(X,Y)$ as $h(X,Y)Y$ for some smooth function h;

(ii) g is decreasing in Y; and

(iii) $h(X,Y)X = g(X,Y)X/Y$ is increasing in X.

Then, $\mathcal{R}(X,Y) = h(X,Y)X$ will have all the properties of the reproduction function $\mathcal{R} = \beta cDX/(X+Y)$ that we have used in this section.

This analysis of homogeneous populations provides the reason for obtaining equations in the forms of (37) and (39) for *heterogeneous* populations. For more general models, the Lyapunov function becomes a sum of terms in the form of (13) or (23). The individual terms are the contributions of the population subgroups to the Lyapunov function. Thus the analysis can proceed in terms of reproduction functions and basic reproduction numbers of the individual subgroups and their interaction in a sum to give the overall population effect.

6. The extremes: Restricted and proportional mixing. Insofar as mixing between population subgroups is concerned, restricted and proportional mixing represent extreme cases. In restricted mixing, there are no disease-transmitting contacts between the subgroups; all contacts of the members of a subgroup are with other members of the same subgroup. Restricted mixing is the pure case of positive assortative mixing, that is, like-with-like mixing. Restricted mixing means the population is made up of isolated, homogeneous subpopulations. In proportional mixing, on the other hand, contacts between individuals in all subgroups are at random; that gives proportional mixing between subgroups. All other types of mixing impose some restrictions on randomness of mixing within the population as a whole, and so fall between restricted and proportional mixing. For that reason, we first look at the behavior of these extremes.

6.1. Restricted mixing. For restricted mixing we need not separately consider the cases with and without deaths due to the disease; the analysis is the same for both.

6.1.1. One infectious stage. The derivative of the Lyapunov function $V = \sum_i c_i\beta_i DY_i$ is given by:

$$\dot{V} = \sum_i \Big(\frac{c_i\beta_i DX_i}{N_i} - 1\Big)\frac{V_i}{D} = \sum_i (\mathcal{R}_i - 1)\frac{V_i}{D}. \tag{41}$$

In this case, $\mathcal{R}_i$ is a function of X_i and Y_i only, and there is no interaction between the subgroups. We can work with each $\dot{V}_i = (\mathcal{R}_i - 1)V_i/D$ for each subpopulation i separately. Regardless of whether there are deaths due to the disease, $\mathcal{R}_i = c_i\beta_i DX_i/(X_i + Y_i)$ takes on its maximum value at $X_i = U_i/\mu$, where it becomes the basic reproduction number. Thus the analysis of this case is the same as the analysis of a number of simultaneous cases of the homogeneous population in §5.3, and we can conclude that if

$$\frac{c_i\beta_i}{\mu + k} - 1 = R_{oi} - 1 < 0,$$

then the disease-free equilibrium for subpopulation i is globally stable. The disease-free state for the population as a whole is globally stable only if the corresponding equilibria of all the population subgroups are globally stable. On the other hand, if

$$R_{oi} - 1 > 0, \tag{42}$$

holds, then the disease-free equilibrium is unstable, and we have global stability of the unique endemic equilibrium for subgroup i. Now we can have mixtures of globally stable endemic equilibria for some subgroups and disease-free equilibria for others, all giving globally stable population equilibria for which $\dot{V} = 0$ because $\dot{V}_i = 0$ for all i.

6.1.2. Multiple infectious stages. The dynamics for subpopulation i under restricted mixing with multiple stages of infection is given by the system

$$\begin{aligned}
\dot{X}_i &= -\frac{c_i X_i \sum_r \beta_{ir} Y_{ir}}{X_i + \sum_r Y_{ir}} + U_i - \mu X_i,\\
\dot{Y}_{i1} &= +\frac{c_i X_i \sum_r \beta_{ir} Y_{ir}}{X_i + \sum_r Y_{ir}} - (\mu + k)Y_{i1},\\
\dot{Y}_{ij} &= kY_{i(j-1)} - (\mu + k)Y_{ij}, \qquad \text{for } j = 2, \cdots, m.
\end{aligned} \tag{43}$$

The multistage Lyapunov function is

$$V_i = \frac{c_i}{k + \mu}\sum_{r=1}^{m}\sum_{p=r}^{m}\beta_{ip}\left(\frac{k}{k+\mu}\right)^{p-r} Y_{ir} = \frac{c_i}{k+\mu}\sum_{r=1}^{m} b_{ir}Y_{ir}, \tag{44}$$

as in (23), (25), with

$$\dot{V}_i = \left(\frac{c_i\bar{\beta}_i\hat{D}X_i}{X_i + Y_i} - 1\right)c_i\sum_r \beta_{ir}Y_{ir} = \left(\frac{c_i b_{i1} D_1 X_i}{X_i + Y_i} - 1\right)c_i\sum_r \beta_{ir}Y_{ir} \tag{45}$$

for each i.

Again, $\mathcal{R}_i = c_i\bar{\beta}_i\hat{D}X_i/(X_i+Y_i)$ is increasing in X_i, decreasing in Y_i, and takes on its maximum value at $X_i = U_i/\mu, Y_i = 0$. If

$$c_i\bar{\beta}_i\hat{D} - 1 = R_{oi} - 1 < 0,$$

then $\mathcal{R}_i - 1 < 0$ and $\dot{V}_i < 0$ everywhere in the interior of B, and the disease-free equilibrium is globally stable for subpopulation i, just as in the case of only one stage of infection.

We turn now to considerations of the global stability of the endemic equilibrium for the restricted mixing models under discussion. Even though the function V in (44) is a Lyapunov function only for the disease-free equilibrium, it can be very helpful in the analysis of the endemic equilibrium. Since the subgroups are isolated from each other in restricted mixing, we work with each subgroup separately and drop the subscript i.

First, note that if we write (43) for restricted mixing in terms of the $(m+1)$ variables $N, V, Y_2, \cdots, Y_m$, we obtain the following system that is "almost linear:"

$$\begin{aligned}
\dot{N} &= U - \mu N - kY_m,\\
\dot{V} &= \frac{c\sum_r b_rY_r}{N}\big[(cb_1D_1 - 1)N - V + cD_1(b_2 - b_1)\,Y_2\\
&\qquad + cD_1(b_3 - b_1)\,Y_3 + \cdots + cD_1\,(b_m - b_1)\,Y_m\big],\\
\dot{Y}_2 &= \frac{1}{b_1D_1}\left(\frac{k}{c}V - (b_1 + kD_1b_2)\,Y_2 - kD_1b_3Y_3 - \cdots - kD_1b_mY_m\right), \qquad (46)\\
\dot{Y}_3 &= \quad kY_2 - \frac{1}{D_1}Y_3,\\
&\ \ \vdots \qquad\quad \vdots\\
\dot{Y}_m &= \quad kY_{m-1} - \frac{1}{D_1}Y_m,
\end{aligned}$$

where $D_1 = 1/(\mu + k)$ is the mean duration of one stage and

$$b_r \equiv \beta_r + kD_1\beta_{r+1} + \cdots + (kD_1)^{m-r}\beta_m,$$

as in expression (24). Only the factor $c\sum b_rY_r/N$ in the expression for $\dot{V}$ keeps this representation (46) of system (43) from being linear, and this factor is strictly positive at the endemic equilibrium.

For some values of the parameters, we can use the $m+1$ linearly independent functions $N, V, Y_2, \cdots, Y_m$ to construct a parameterized family of invariant boxes about the endemic equilibrium, as we did in Fig. 5 for $m = 1$. This construction implies the global stability of the endemic equilibrium. We will carry out this construction for $m = 2$ here and present the proof for general m in Appendix A. The first part of Theorem 2 summarizes the remarks at the beginning of this section.

THEOREM 2. *Consider system* (1)–(5) *or system* (1a)–(5a) *with restricted mixing:* $g_i = c_i\sum_r \beta_{ir}Y_{ir}/(X_i+Y_i)$, *with m stages of infection, with or without death from the disease. In this case, we can work with each subpopulation separately, as in system* (43).

(a) *If* $R_{oi} = \bar{\beta}_ic_i\hat{D} < 1$, *then the disease-free equilibrium is unique and globally asymptotically stable for subpopulation i, with* $V_i = c_i\bar{\beta}_i\hat{D}Y_i$ *a global Lyapunov function.*

(b) *Suppose that* $m = 2$, *that is; the disease passes through two stages. For any specific subpopulation, suppose that* $R_0 = \bar{\beta}\hat{D}c > 1$, *so that its disease-free equilibrium is unstable and it has a unique endemic equilibrium. Suppose further that for this subpopulation*

$$\frac{\bar{\beta}\hat{D}c - 1}{\bar{\beta}\hat{D}c} \leq \frac{\mu}{k}\left(\frac{\mu}{k} + 2\min\left\{1, \frac{b_2}{b_1}\right\}\right). \tag{47}$$

Then, the unique endemic equilibrium of this subpopulation is globally asymptotically stable.

Proof of Theorem 2(b). Let $(X^*, \mathbf{Y}^*) = (X^*, Y_1^*, Y_2^*)$ be the endemic equilibrium that exists because $R_o = \bar{\beta}c\hat{D} = b_1 c D_1 > 1$. Let $N^* = N(X^*, \mathbf{Y}^*)$ and $V^* = V(X^*, \mathbf{Y}^*)$. For each $\varepsilon > 0$, consider the box B_ε defined by the following inequalities:

$$\begin{aligned} N^* - \varepsilon\frac{k}{\mu} \leq N(X, \mathbf{Y}) &\leq N^* + \varepsilon\frac{k}{\mu}, \\ V^* - \varepsilon v \leq V(X, \mathbf{Y}) &\leq V^* + \varepsilon v, \\ Y_2^* - \varepsilon \ \leq Y_2 \ &\leq \ Y_2^* + \varepsilon, \end{aligned} \tag{48}$$

where $v \equiv c(b_1 + kD_1 b_2)/k$.

The proof verifies that the vector field determined by the system (43), (46) of differential equations points into B_ε on its boundary sides. For example, when $Y_2 = Y_2^* + \varepsilon$, then using (46), the fact that $\dot{Y}_2(X^*, \mathbf{Y}^*) = 0$, and the definition of v, we have

$$\begin{aligned} \dot{Y}_2 &= \frac{1}{b_1 D_1}\left(\frac{k}{c}V - (b_1 + kD_1 b_2)(Y_2^* + \varepsilon)\right) \\ &\leq \frac{1}{b_1 D_1}\left(\frac{k}{c}(V^* + \varepsilon v) - (b_1 + kD_1 b_2)(Y_2^* + \varepsilon)\right) \\ &= 0 + \varepsilon\frac{k}{b_1 c D_1}\left[v - \frac{c}{k}(b_1 + b_2 k D_1)\right] \\ &= 0. \end{aligned} \tag{49}$$

Similarly, we show that $\dot{N} \leq 0$ when $N = N^* + \varepsilon k/\mu$ and that $\dot{V} \leq 0$ when $V = V^* + \varepsilon v$. The first of these is straightforward; the second uses the expression for $\dot{V}$ in (46) and also hypothesis (47). See the proof of the more general Theorem 3 in Appendix A for details.

Let $F(X, Y_1, Y_2) = \max\{\mu/k\|N - N^*\|, 1/v\|V - V^*\|, \|Y_2 - Y_2^*\|\}$. For any positive ε, the set of $\{(X, Y_1, Y_2) : F(X, Y_1, Y_2) \leq \varepsilon\}$ is just the box B_ε of (48). The argument in the previous paragraph shows that $\dot{F} < 0$ on $F = \varepsilon$, except perhaps on the lower–dimensional edges where F is not smooth. Since (X^*, Y_1^*, Y_2^*) is a strict global minimum of F, it follows that F is a Lyapunov function, which proves the global stability of (X^*, Y_1^*, Y_2^*). See Lajmanovich and Yorke [5] for reassurance that there is no problem with the nonsmoothness of F on a lower-dimensional complex. □

We now present the statement of the corresponding theorem for general m. We present the proof of Theorem 3, below, in Appendix A.

THEOREM 3. *Consider the* SI *model* (1), (3)–(5) *or* (1a), (3a)–(5a) *with restricted mixing as in the hypothesis of Theorem* 2, *and with* m *stages of infection. Focus on a*

single population, say population i, as described by system (43), *but drop the subscript i for simplicity of notation. Let $b_1, \cdots b_m$ be combinations of the β_r's as in* (24) *and let*

$$\alpha \equiv kD_1 = k/(\mu + k).$$

Suppose that $R_0 = \bar{\beta}\hat{D}c = b_1 D_1 c > 1$, so that the disease-free equilibrium is unstable. Suppose further that

$$\left(\frac{b_1 D_1 c - 1}{D_1 c}\right) \leq \frac{\mu}{k}\left(1 + \frac{\mu}{k}\right)^{m-1} \cdot \Big[b_1 + \alpha(b_2 - |b_1 - b_2|) - \alpha^2(b_3 + |b_1 - b_3|) - \alpha^3(b_4 + |b_1 - b_4|) - \cdots - \alpha^{m-1}(b_m + |b_1 - b_m|)\Big]. \tag{50}$$

Then the unique endemic equilibrium of the subpopulation under consideration is globally asymptotically stable.

Hypothesis (50) reduces to hypothesis (47) when $m = 2$. Lin [21] provides a longer proof that the endemic equilibrium is globally stable under the hypothesis that $\mu > k$. However, for models of HIV spread, k is greater than μ. For two stages of infection, the hypothesis (47) of Theorem 2 is clearly weaker than the corresponding hypothesis in [21] and includes situations where $k > \mu$. It is true, however, that conditions (47) and (50) are more readily satisfied the bigger μ is relative to k. For example, under the reasonable hypothesis that $b_1 \geq b_i$ for all i, (50) becomes

$$\left(\frac{b_1 D_1 c - 1}{b_1 D_1 c}\right) \leq \left(1 + \frac{\mu}{k}\right)^m \cdot \left[1 - 2\alpha + \alpha^m + \frac{2b_2}{b_1}\alpha(1 - \alpha)\right],$$

as we demonstrate in Appendix A.

6.2. Proportional mixing. For proportional mixing there is a great difference in the analysis depending on whether there is death due to the disease. Expressions (15) and (30) can be reduced to the corresponding expressions for proportional mixing by noting that there is then only one activity group.

For proportional mixing with one stage of infection, the derivative of the Lyapunov function V is

$$\dot{V} = \sum_i \left(\frac{\sum_j c_j^2 \beta_j D X_j}{\sum_j c_j N_j} - 1\right)\frac{V_i}{D}.$$

In this case, the coefficients of V_i are independent of i and are the same for all i, so $\dot{V}$ can be written as

$$\dot{V} = \left(\frac{\sum_j c_j^2 \beta_j D X_j}{\sum_j c_j N_j} - 1\right)\frac{V}{D}. \tag{51}$$

In this case, we obtain a population reproduction function

$$\mathcal{R}(X_1, \cdots, Y_n) = \frac{\sum_j c_j^2 \beta_j D X_j}{\sum_j c_j N_j}. \tag{52}$$

At the disease-free equilibrium, $\mathcal{R}$ becomes

$$\mathcal{R}_o = \mathcal{R}\left(\frac{U_1}{\mu}, \cdots, \frac{U_n}{\mu}, 0, \cdots, 0\right) = \frac{\sum_j c_j^2 \beta_j D U_j}{\sum_j c_j U_j} = \frac{\sum_j c_j U_j (c_j \beta_j D)}{\sum_j c_j U_j}. \tag{53}$$

6.2.1. No deaths due to the disease and one infectious stage. The analysis of proportional mixing is especially straightforward for models with no disease-related deaths.

Case 1. ($\mathcal{R}_o - 1 \leq 0$). Since each N_j is constant on the stable invariant set (6) of Proposition 1, $\mathcal{R}$ does not depend on any Y_j's and is easily seen to be strictly increasing in each X_j. Therefore, $\mathcal{R}$ takes on its maximum value at the corner of the invariant set (6), where each X_j takes on its maximum value U_j/μ. If $\mathcal{R}_o - 1 \leq 0$, $\mathcal{R}(X,Y) - 1 < 0$ for all (X,Y) in the set (6). By (51), $\dot{V} < 0$ throughout the interior of invariant set (6), and V is a Lyapunov function for the global stability of the no–disease equilibrium. Thus $\mathcal{R}_o - 1 \leq 0$ is a necessary and sufficient condition for global stability of the disease-free equilibrium. As a result, $\mathcal{R}_o$ in (53) is the threshold for the stability of the disease-free equilibrium and for the existence of the endemic equilibrium. (This simple proof carries over directly to SIS, SIR, and SIRS heterogeneous populations without deaths due to the disease.)

If $\mathcal{R}_o - 1 > 0$, the disease-free equilibrium is unstable and there is persistence of an endemic state.

Expression (53) shows that the mean basic reproduction number $\mathcal{R}_o$ for proportional mixing is a weighted average of the classical reproduction numbers $R_{oj} = c_j \beta_j D$. We can write $\mathcal{R}_o - 1$ as

$$\mathcal{R}_o - 1 = \frac{\sum_j c_j U_j [c_j D \beta_j - 1]}{\sum_j c_j U_j}. \tag{54}$$

It is of interest to see how the thresholds $R_{oj} - 1$ on the individual subgroups contribute to the overall threshold $\mathcal{R}_o - 1$. We present three cases.

(1) If $c_j D \beta_j - 1 \leq 0$, for all j, we have a sufficient but not necessary condition for global stability of the disease-free equilibrium.

(2) If $c_j D \beta_j - 1 > 0$, for all j, we have a sufficient but not necessary condition for persistence of the endemic state.

(3) It is possible for the basic reproduction number for some subgroups to be less than one and for other subgroups to be greater than one. The necessary and sufficient condition for global stability of the disease-free equilibrium is that the *weighted* sum $\mathcal{R}_o$ be ≤ 1. Note the role of the weights $c_j U_j$ in (54). For the same distribution of the $c_j D \beta_j$'s, one distribution of sizes of the subgroups (U_j/μ) may give global stability of the disease-free equilibrium, while another may give persistence of an endemic state!

6.2.2. No deaths due to the disease: multiple infectious stages. If we include multiple stages of infection, still with no disease-related deaths, the equation for $\dot{V}$ becomes

$$\dot{V} = \left(\frac{\sum_j c_j^2 \bar{\beta}_j D X_j}{\sum_j c_j N_j} - 1 \right) \sum_i \sum_r c_i \beta_{ir} Y_{ir}. \tag{55}$$

The expression for $\mathcal{R}$ is the same as in (51) with the usual change in the meaning of the parameters D and $\bar{\beta}_j$. Once again, $(\mathcal{R} - 1)$ factors completely out of the expression for $\dot{V}$; and the analysis is identical to that for $m = 1$ given in the previous subsection.

The following theorem summarizes our results in §§6.2.1 and 6.2.2.

THEOREM 4. *Consider system* (1)–(5) *with proportional mixing, with any number of stages m of infection, and with no disease–related deaths. Define* $V = D \sum_{i,r} c_i \bar{\beta}_i Y_{ir}$. *Then,* $\dot{V} = (\mathcal{R} - 1)V/D$, *where* $\mathcal{R}$ *is the reproduction function* (52). *If the mean basic*

reproduction number $\mathcal{R}_o$ in (53) *is < 1, then the disease-free equilibrium is globally asymptotically stable, with V a global Lyapunov function. If $\mathcal{R}_o > 1$, the disease-free equilibrium is unstable.*

6.2.3. Deaths due to the disease: one infectious stage. The analysis becomes more delicate when we consider disease–related deaths. We begin with the case where $m = 1$. As we compute in (51), the derivative $\dot{V}$ is now

$$\dot{V} = \left(\frac{\sum_j c_j^2 \beta_j X_j}{(k+\mu)\sum_j c_j N_j} - 1 \right) \sum_i c_i \beta_i Y_i = [\mathcal{R} - 1] \sum_i c_i \beta_i Y_i. \tag{56}$$

At the disease-free equilibrium, if

$$\frac{1}{k+\mu} \frac{\sum_j c_j^2 \beta_j U_j}{\sum_j c_j U_j} - 1 = \mathcal{R}_o - 1 < 0, \tag{57}$$

then $\dot{V} < 0$ in a neighborhood of the disease-free equilibrium, which immediately implies the local stability of the disease-free equilibrium. However, because $N_j = X_j + Y_j$ is no longer constant, the reproduction function $\mathcal{R}$ is not necessarily monotonically increasing in X_j. As a result, the proof of global stability is now more difficult.

For this case of $m = 1$, we can obtain the same results that we obtained in Theorem 4 for the case of no disease–related deaths. However, to make the proof work, we need to assume that the probability β_i of transmission per contact is the same for all population subgroups i. Expression (57) becomes

$$\mathcal{R}_o - 1 = \frac{\beta \sum_j c_j^2 U_j}{(k+\mu)\sum_j c_j U_j} - 1 \leq 0. \tag{58}$$

We rewrite (56) as

$$\dot{V} = \left(\beta D \sum_j c_j^2 X_j - \sum_j c_j N_j \right) \frac{\beta \sum_i c_i Y_i}{\sum_j c_j N_j}, \tag{59}$$

where $D = 1/(k+\mu)$. Denote the term in parentheses in (59) by

$$W = \beta D \sum_j c_j^2 X_j - \sum_j c_j N_j. \tag{60}$$

Then $\dot{V}$ and W have the same sign in the interior of the invariant region (6). In particular, $\mathcal{R}_o - 1 \leq 0$ if and only if $W(\mathbf{U}/\mu, \mathbf{0}) \leq 0$. Note that $W = 0$ is a hyperplane that separates the $2n$-dimensional (X, Y)-space into two components. To prove global stability of the disease-free equilibrium, we would like to show that when (58) holds, $W < 0$ in the invariant set (6). However, it appears that W can be positive when (58) holds. We can prove that $\dot{W} < 0$ when $W \geq 0$ so that all trajectories eventually move into and then stay inside the region where $W < 0$, that is, where $\dot{V} < 0$. The details of this argument are carried out in Appendix B. The conclusion is summarized in the following theorem.

THEOREM 5. *Consider system* (1a), (2a) *with proportional mixing, with one stage of infection ($m = 1$), and with disease-related deaths. Assume that β_i is independent of i. Define $V = (\beta D)\sum_i c_i Y_i$. Then $\dot{V} = (\mathcal{R} - 1)V/D$, where $\mathcal{R}$ is the reproduction*

function (52). *If the mean basic reproduction number* $\mathcal{R}_o$ *in* (53) *is* < 1, *then the disease-free equilibrium is globally asymptotically stable, with Lyapunov function* V. *If* $\mathcal{R}_o > 1$, *the disease-free equilibrium is unstable.*

6.2.4. Deaths due to the disease: more than one infectious stage. The analysis is more delicate when we allow stages of infection. We can use the idea of the proof of Theorem 5 to give the necessary and sufficient condition for local stability and to derive some sufficient conditions for the global stability of the disease-free equilibrium when $m > 1$.

THEOREM 6. *Consider system* (1a), (3a)–(5a) *with proportional mixing and with multiple stages of infection* ($m > 1$), *and with disease-related deaths. Let* $V(\mathbf{X}, \mathbf{Y})$ *be the function defined in* (23). *Then* $\dot{V}$ *is given by*

$$\dot{V} = \left(\frac{\sum_j c_j^2 \bar{\beta}_j \hat{D} X_j}{\sum_j c_j N_j} - 1 \right) \sum_i \sum_r c_i \beta_{ir} Y_{ir} \equiv [\mathcal{R}(\mathbf{X}, \mathbf{Y}) - 1] \sum_i \sum_r c_i \beta_{ir} Y_{ir}. \tag{61}$$

(a) *If* $\mathcal{R}_o \equiv \mathcal{R}(\mathbf{U}/\mu, \mathbf{0}) < 1$, *then the disease-free equilibrium is locally asymptotically stable.*

(b) *If* $\mathcal{R}_o > 1$, *the disease-free equilibrium is unstable.*

(c) *Suppose that* β_{jr} *depends only on the stage* r *of infection and that*

$$\hat{D}\bar{\beta} \equiv D \sum_{r=1}^{m} \beta_r (kD)^{r-1} < D\beta_m.$$

Then the disease-free equilibrium is globally asymptotically stable.

The proofs of parts (a) and (b) follow immediately from expression (61) of $\dot{V}$. For example, in case (a), $\mathcal{R}_o < 1$ means that $\dot{V}$ is negative on a neighborhood of the disease-free equilibrium, and therefore that V is a Lyapunov function for the disease-free equilibrium. We present the proof of part (c) of Theorem 6 in Appendix B.

Remark. To prove the global stability of the disease-free equilibrium, we assume that the transmission probabilities β are the same for all subpopulations in the one–stage model of Theorem 5 and that β depends only on the stage of infection in the multi-stage model of Theorem 6. Huang, Cooke, and Castillo-Chavez [27], [28] have recently constructed an example of a multipopulation SI-model with proportional mixing in which there are two locally stable equilibria, apparently the disease-free equilibrium and an endemic equilibrium. This unexpected appearance of an equilibrium that is locally but not globally asymptotically stable in these models appears to be driven by the asymmetric manner in which the transmission probabilities β_{ij} depend strongly on the subpopulations i and j.

7. Structured mixing. We turn now to a consideration of the general case of structured mixing with proportional mixing within activity groups. Expressions (11) and (12) present the differential equations for such mixing when there is only one stage of infection; expression (33) gives the formula for the corresponding $\dot{V}$. Note that $\dot{V}$ has the form

$$\dot{V} = \sum_i (\mathcal{R}_i - 1) \frac{V_i}{D},$$

where $\mathcal{R}_i$ is

$$\mathcal{R}_i = \sum_s f_{is} \frac{\sum_j c_j^2 \beta_j D f_{js} X_j}{\sum_j c_j f_{js} N_j}$$

and $\mathcal{R}_{oi}$ is

$$\mathcal{R}_{oi} = \sum_s f_{is} \frac{\sum_j c_j^2 \beta_j D f_{js} U_j}{\sum_j c_j f_{js} U_j}.$$

Thus, (33) gives $\dot{V}$ as a sum over population subgroups of terms $(\mathcal{R}_i - 1)(V_i/D)$, one for each subgroup.

Using the relation $\sum_s f_{is} = 1$, (33) can also be put in the form

$$\dot{V} = \sum_s \Big(\frac{D \sum_j \beta_j c_j^2 f_{js} X_j}{\sum_j c_j f_{js} N_j} - 1 \Big) \frac{\sum_i f_{is} c_i \beta_i D Y_i}{D}. \tag{62}$$

The first factor in the sum in (62) is the reproduction function $\mathcal{R}_s$ for activity group s; the second is the Lyapunov function for activity group s, divided by D. Expression (62) is of the form

$$\dot{V} = \sum_s [\mathcal{R}_s - 1] \frac{V_s}{D}.$$

Thus $\dot{V}$ can be written in two ways: as a sum over population subgroups, or as a sum over activity groups. Furthermore, we note that $\mathcal{R}_i$ is a weighted sum of the $\mathcal{R}_s$:

$$\mathcal{R}_i = \sum_s f_{is} \mathcal{R}_s$$

7.1. No deaths due to the disease. When there are no deaths due to the disease, we can, as usual, consider $N_j = X_j + Y_j$ as equaling the constant population size U_j/μ. In this case, each $\mathcal{R}_j$ is either strictly increasing in X_j or it does not depend on X_j, i.e., $f_{js} = 0$. In the invariant region (6), each $\mathcal{R}_j$ has its maximum at the disease-free equilibrium. We immediately obtain the following results.

(1) If $\mathcal{R}_{oi} - 1 \leq 0$ for all i, then each $\mathcal{R}_i$ is < 1 throughout region (6) and $\dot{V} < 0$ throughout (6). In this case, the disease-free equilibrium is globally asymptotically stable.
(2) If $\mathcal{R}_{oi} - 1 > 0$ for all i, we have a sufficient but not necessary condition for persistence of an endemic state.
(3) If $\mathcal{R}_{os} \leq 1$ for all s, then $\mathcal{R}_{oi} \leq 1$ for all i since $\mathcal{R}_i = \sum_s f_{is} \mathcal{R}_s$, and the disease-free equilibrium is globally asymptotically stable.
(4) If $\mathcal{R}_{os} > 1$ for all s, then $\mathcal{R}_{oi} > 1$ for all i and an endemic state persists.
(5) The most interesting case is the mixed case in which for some i, $\mathcal{R}_{oi} - 1 < 0$ and for others $\mathcal{R}_{oi} - 1 > 0$. In some cases this gives local stability, but in others it gives an unstable disease-free equilibrium, all depending on the sign of $\dot{V}$.

7.2. Disease-related deaths. In the case of disease-related deaths, $N_i = X_i + Y_i$ is no longer constant. As we have seen earlier, this means that the reproduction functions $\mathcal{R}_i$ are no longer linear in the X_j's and no longer have a guaranteed global maximum at the disease-free equilibrium. However, we can still conclude that

(1) If each $\mathcal{R}_{oi} < 1$, then $\dot{V}$ is negative on an open set in the interior of B at the disease-free equilibrium. Therefore, the disease-free equilibrium is locally asymptotically stable.
(2) If each $\mathcal{R}_{oi} > 1$, then $\dot{V}$ is positive arbitrarily close to the disease-free equilibrium, and this equilibrium is unstable.

(3) If the reproduction number $R_{oj} = \beta_j c_j D < 1$ for all j, then the disease-free equilibrium is globally asymptotically stable. To see this, rewrite expression (62) for $\dot{V}$ as

$$\dot{V} = \sum_s \left(\sum_j (\beta_j c_j D - 1)(c_j f_{js} X_j) - \sum_j (c_j f_{js} Y_j) \right) \frac{\sum_i \beta_i c_i f_{is} Y_i}{\sum_i c_i f_{is} N_i}.$$

If $\beta_j c_j D < 1$ for all j, then $\dot{V}$ is negative whenever $\mathbf{Y} \neq \mathbf{0}$, and V is a global Lyapunov function for the stability of the disease-free equilibrium.

The challenge is to adapt this approach to find a necessary and sufficient condition for the stability of the disease-free equilibrium so that a single threshold can be computed. To provide some insight for the proper adaptation, we now look at two special cases of structured mixing: geographic mixing and preferred mixing.

7.3. Geographic mixing. We assume in this section that the infection probabilities β_i and the contact rates c_i are the same for all groups. We call this "geographic mixing" in analogy with a situation in which a population is distributed over a number of distinct geographic sites, but the population is otherwise uniform in characteristics such as the mean contact rate per person. Some persons travel so there is mixing at the different sites. Now, (33) becomes:

$$\dot{V} = \sum_i \left[c\beta D \sum_s f_{is} \frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} - 1 \right] c\beta Y_i. \tag{63}$$

Note that $R_o = c\beta D$ for all population subgroups. At the disease-free equilibrium, the term in brackets in (63) reduces to $R_o - 1$. Rewrite (63) as

$$\begin{aligned} \dot{V} &= \sum_i \left[R_o \sum_s f_{is} \frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} - 1 \right] c\beta Y_i \\ &= \sum_i \sum_s f_{is} \left[R_o \frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} - 1 \right] \frac{V_i}{D}, \end{aligned}$$

since $\sum_s f_{is} = 1$. If $R_o - 1 \leq 0$, then

$$R_o \frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} - 1 \leq 0$$

because

$$\frac{\sum_j f_{js} X_j}{\sum_j f_{js} N_j} \leq 1.$$

Furthermore, the equality sign holds only at the disease-free equilibrium $X_j = N_j = U_j/\mu$ for all j. It follows that if $R_o - 1 \leq 0$ for geographic mixing, the disease-free equilibrium is globally stable, regardless of whether there are deaths due to the disease.

By continuity, there is some range of variation in the c_i's around a mean value for which there will be global stability for the disease-free equilibrium when the mean $R_o - 1$ is less than zero.

8. Preferred mixing. Preferred mixing is one fairly general form of structured mixing that has been used in epidemiological models. See, for example, Nold [29],

Hethcote, Yorke, and Nold [30], Hethcote and Van Ark [19], and Jacquez et al. [15]. For preferred mixing, the fraction ρ_{ij} of population subgroup i's contacts that are with subgroup j is given by

$$\rho_{ij} = \begin{cases} r_i + (1-r_i)\dfrac{(1-r_i)c_iN_i}{\sum_h (1-r_h)c_hN_h}, & i = j, \\ (1-r_i)\dfrac{(1-r_j)c_jN_j}{\sum_h (1-r_h)c_hN_h}, & i \neq j. \end{cases}$$

The parameter r_i can be considered as the fraction of group i's contacts that are reserved for within-group activities. If $r_i = 1$, group i is experiencing restricted mixing; if $r_i = 0$, group i participates fully in proportional mixing. Jacquez et al. [15] study the impact of the value of r_i on the behavior of the epidemiological model under study. As we mentioned in §3, preferred mixing is a form of structured mixing with $M = n+1$ activity groups, $f_{ii} = r_i$, $f_{i,n+1} = 1 - r_i$, $f_{is} = 0$ for $s \neq i$ and $s \neq n+1$, and proportional mixing in the $(n+1)$th activity group.

It proves to be advantageous to include the mixing in the Lyapunov function V for preferred mixing. In particular, let

$$V(\mathbf{X}, \mathbf{Y}) = \frac{1}{\mu + k} \sum_i \frac{c_i(1-r_i)}{1 - c_i r_i \bar{\beta}_i \hat{D}} \sum_r b_{ir} Y_{ir}, \tag{64}$$

where b_{ir} is the combination of the β_{ip}'s given in (24). It is shown explicitly in Lin [21] and implicitly in Jacquez et al. [15] that the denominator of V in (64), $1 - c_i r_i \bar{\beta}_i \hat{D}$, must be positive for the disease-free equilibrium to be locally stable. As we show in Appendix C, for V as in (64), V factors completely out of the expression for $\dot{V}$ so that we can write $\dot{V}$ as:

$$\dot{V} = (\mathcal{R} - 1 - E)V^*, \tag{65}$$

where

$$\mathcal{R} \equiv \frac{\sum_j \dfrac{c_j^2(1-r_j)^2 \bar{\beta}_j \hat{D} X_j}{1 - c_j r_j \bar{\beta}_j \hat{D}}}{\sum_j c_j(1-r_j)N_j}, \tag{66}$$

$$E \equiv \frac{\sum_j \dfrac{c_j^2(1-r_j) r_j \bar{\beta}_j \hat{D} Y_j (\sum_r \beta_{jr} Y_{jr})/N_j}{1 - c_j r_j \bar{\beta}_j \hat{D}}}{\sum_j c_j(1-r_j) \sum_r \beta_{jr} Y_{jr}}, \tag{67}$$

$$V^* \equiv \sum_j c_j(1-r_j) \sum_r \beta_{jr} Y_{jr}.$$

At the disease-free equilibrium ($X_i = U_i/\mu, Y_{ir} = 0$ for all i, r),

$$\mathcal{R}\left(\frac{\mathbf{U}}{\mu}, \mathbf{0}\right) = \mathcal{R}_o = \frac{\sum_j \dfrac{c_j^2(1-r_j)^2 \bar{\beta}_j \hat{D} U_j}{1 - c_j r_j \bar{\beta}_j \hat{D}}}{\sum_j c_j(1-r_j)U_j} \tag{68}$$

$$= \sum_j \left(\frac{c_j(1-r_j)U_j}{\sum_h c_h(1-r_h)U_h}\right)\left(\frac{1-r_j}{1 - c_j r_j \bar{\beta}_j \hat{D}}\right)\left(c_j \bar{\beta}_j \hat{D}\right) \tag{69}$$

and

$$E\left(\frac{\mathbf{U}}{\mu}, \mathbf{0}\right) = 0. \tag{70}$$

As we show in Appendix C, E in (67) is continuous at $\mathbf{Y} = \mathbf{0}$ because its numerator is a positive *quadratic* in the Y_{ij}'s and its denominator is a positive *linear* function in the Y_{ij}'s. It follows from the continuity of E and from (65) and (70) that the basic reproduction number $\mathcal{R}_o$ is the stability threshold for the disease-free equilibrium. If $\mathcal{R}_o < 1$, then $\mathcal{R} - 1 - E$ will be negative in an open set about the disease-free equilibrium. This implies by (65) that $\dot{V} < 0$ in the intersection of this open set and the interior of the positive orthant. Therefore, $\mathcal{R}_o < 1$ implies that the disease-free equilibrium is locally asymptotically stable. Similarly, if $\mathcal{R}_o > 1$, the disease-free equilibrium is unstable.

Note that the decomposition of $\mathcal{R}_o$ in (69) is similar to the decomposition in (36b). The third factor in (69) is the classical basic reproduction number, and the first factor in (69) is the population weight in the weighted average. The new wrinkle is the middle factor in (69), a term that considers the mixing in the population under study.

We can use (65) and (66) to derive sufficient conditions for the *global* stability of the disease-free equilibrium under preferred mixing. Combining (65) and (66) and using the fact that $E \geq 0$, we find that

$$\dot{V} \leq \left(\frac{\displaystyle\sum_j \frac{c_j^2(1-r_j)^2 \bar{\beta}_j \hat{D} X_j}{1 - c_j r_j \bar{\beta}_j \hat{D}}}{\sum_j c_j(1-r_j)N_j} - 1 \right) \cdot \sum_i c_i(1-r_i) \sum_r \beta_{ir} Y_{ir}$$

$$= \left[\sum_j \frac{c_j^2(1-r_j)^2 \bar{\beta}_j \hat{D} X_j}{1 - c_j r_j \bar{\beta}_j \hat{D}} - \sum_j c_j(1-r_j)N_j \right] \left(\frac{\sum_i c_i(1-r_i) \sum_r \beta_{ir} Y_{ir}}{\sum_i c_i(1-r_i)N_i} \right) \tag{71}$$

$$= \left[\sum_j \frac{c_j(1-r_j)}{1 - c_j r_j \bar{\beta}_j \hat{D}} \left((c_j \bar{\beta}_j \hat{D} - 1) X_j - (1 - c_j r_j \bar{\beta}_j \hat{D}) Y_j \right) \right] \cdot \left(\frac{\sum_i c_i(1-r_i) \sum_r \beta_{ir} Y_{ir}}{\sum_i c_i(1-r_i)N_i} \right) \tag{72}$$

$$\equiv W(\mathbf{X}, \mathbf{Y}) \cdot \left(\frac{\sum_i c_i(1-r_i) \sum_r \beta_{ir} Y_{ir}}{\sum_i c_i(1-r_i)N_i} \right), \tag{73}$$

where W is the expression in square brackets on line (71) or (72). If $c_j \bar{\beta}_j \hat{D} < 1$ for all j, then all the coefficients of the linear function W are negative. In this case, W, and therefore $\dot{V}$, is negative throughout the positive orthant. The function V is a global Lyapunov function for the stability of the disease-free equilibrium.

Moreover, the function W in (71) or (72) plays the same role for preferred mixing that W in (60) plays for proportional mixing. In particular, if there is only one stage of infection and if the β_i's are all equal, then a straightforward modification of the

analysis of W for proportional mixing in Appendix B shows that $\dot{W} < 0$ when $W \geq 0$. We merely replace c_j by $c_j(1-r_j)$ and retain the $1-c_j r_j \bar{\beta}_j \hat{D}$ denominator throughout the analysis of $\dot{W}$ in Appendix B. As a result, when $m = 1$ and the β_j's are equal, $\mathcal{R}_o < 1$ implies that the disease-free equilibrium is globally asymptotically stable. For multiple stages of infection ($m > 1$), the proof of Theorem 6(c) in Appendix B also extends in a straightforward manner to preferred mixing.

The following theorem summarizes the results of this section.

THEOREM 7. *Consider system* (1)–(5) *or* (1a)–(5a) *with preferred mixing. Let* $V(\mathbf{X}, \mathbf{Y})$ *be the function defined in* (64), *with reproduction function* $\mathcal{R}(\mathbf{X}, \mathbf{Y})$ *as defined in* (66) *and basic reproduction function* $\mathcal{R}_o \equiv \mathcal{R}(\mathbf{U}/\mu, \mathbf{0})$ *as defined in* (68). *Then* V *is a Lyapunov function for the stability of the disease-free equilibrium.*

(a) *If* $\mathcal{R}_o < 1$, *then the disease-free equilibrium is locally asymptotically stable.*

(b) *If* $\mathcal{R}_o > 1$, *the disease-free equilibrium is unstable.*

(c) *If* $m = 1$ *and the* β_j*'s are all equal, then* $\mathcal{R}_o < 1$ *implies that the disease-free equilibrium is globally asymptotically stable.*

(d) *If* $m > 1$, *if* β_{jr} *depends only on the stage* r *of infection and if*

$$\hat{D}\bar{\beta} \equiv D \sum_{r=1}^{m} \beta_r (kD)^{r-1} < D\beta_m,$$

then, the disease-free equilibrium is globally asymptotically stable.

(e) *If* $c_j \bar{\beta}_j \hat{D} < 1$ *for all* j, *then the disease-free equilibrium is globally asymptotically stable.*

9. Discussion and Summary. In this paper, we have nearly completed the stability analysis of the disease-free equilibria that was begun in Jacquez et al. [15] for SI models with disease-related deaths, multiple stages of infection, and heterogeneous populations. We developed a threshold for the existence of an endemic equilibrium for restricted, proportional and preferred mixing; see Tables 1 and 2 in [15]. In this paper, we have shown that these thresholds also determine the local stability of the disease-free equilibrium. Lin [21] accomplishes this result, too, but we believe that the approach of this paper has some distinct advantages. First, we obtain results on the *global* stability of the disease-free equilibrium and, at least for restricted mixing, more general results on the stability of the endemic equilibrium.

More importantly, we present a procedure that provides a natural link between the stability of the disease-free equilibrium and the basic reproduction numbers of the disease. This procedure centers around the use of the total number of infectious contacts as a Lyapunov function V for the stability of the disease-free equilibrium. Our procedure presents an alternative to using ad hoc methods to calculate the eigenvalues of the Jacobian derivative matrix of the system at the disease-free equilibrium. We emphasize the main points.

(1) The total number of infectious contacts of the infecteds forms a general Lyapunov function V for checking the stability of the disease-free equilibrium.

(2) For homogeneous populations, this test immediately gives the thresholds in terms of the classical basic reproduction numbers $R_o = \beta c D$.

(3) For heterogeneous populations, the thresholds depend on reproduction functions $\mathcal{R}$, which play the same role that the classical reproduction numbers (really, functions) play for homogeneous populations. Furthermore, when evaluated at the disease-free equilibrium, these reproduction functions become weighted means of the classical basic reproduction numbers of the population subgroups $R_{oj} = c_j \beta_j D$.

It is, of course, true that if $R_{oj} = c_j\beta_j D < 1$ for all j, the disease-free equilibrium is locally stable and if $R_{oj} > 1$ for all j, it must be unstable. However, for such heterogeneous populations, it is possible to have $R_{oj} < 1$ for some j and $R_{oj} > 1$ for others and to have either locally stable or unstable disease-free equilibria. Then, for the same distribution of values of the R_{oj}, stability or instability is determined by the relative recruitment rates for the population subgroups (which determines the relative sizes of the population subgroups close to the disease-free equilibrium) and the pattern of mixing. The Lyapunov function tells us which one occurs.

From an epidemiological viewpoint, what happens in these two situations in which $R_{oj} < 1$ for some j and $R_{oj} > 1$ for others?

(1) The disease-free equilibrium is stable. The disease dies out after the introduction of infecteds because the spread from groups with $R_{oj} > 1$ is dissipated in groups with $R_{oj} < 1$. In effect, the chain of transmission is broken because the effect of the groups that have $R_{oj} < 1$ dominates.

(2) The disease becomes endemic. Significant endemic levels are maintained in some groups that have $R_{oj} > 1$, and very low endemic levels are found in groups with $R_{oj} < 1$, because the groups with $R_{oj} > 1$ not only maintain infection within themselves but they also constantly seed the groups with $R_{oj} < 1$. The disease would die out in the latter if they were isolated from the rest of the population.

This epidemiological insight suggests another approach to the problem: to examine chains of transmission in terms of the basic reproduction numbers. That approach is for future work.

In addition, we have found that, for restricted mixing, using the functions N and V as coordinate functions enables us to nearly linearize the system and allows us to construct a natural Lyapunov function for the stability of the endemic equilibrium.

Appendix A. Proof of Theorem 3. The proof of Theorem 3 follows the pattern of the proof of Theorem 2(b) for $m = 2$. Let $(X^*, \mathbf{Y}^*)$ be the unique endemic equilibrium, which exists because $\mathcal{R}_o = b_1 c D_1 > 1$. As before, let $N^* = N(X^*, \mathbf{Y}^*)$, $V^* = V(X^*, \mathbf{Y}^*)$, and $\alpha = k/(\mu + k) = kD_1$. For each $\varepsilon > 0$, consider the box B_ε defined by the following inequalities:

$$
\begin{aligned}
N^* - \varepsilon\frac{k}{\mu} \;&\le\; N(X, \mathbf{Y}) \;\le\; N^* + \varepsilon\frac{k}{\mu}, \\
V^* - \varepsilon w \;&\le\; V(X, \mathbf{Y}) \;\le\; V^* + \varepsilon w, \\
Y_2^* - \frac{\varepsilon}{\alpha^{m-2}} \;&\le\; Y_2 \;\le Y_2^* + \frac{\varepsilon,}{\alpha^{m-2}}, \\
&\vdots \quad\; \vdots \quad\; \vdots \\
Y_m^* - \varepsilon \;&\le Y_m \;\le\; Y_m^* + \varepsilon,
\end{aligned}
\tag{A1}
$$

where

$$
w \equiv \frac{cD_1}{\alpha^{m-1}}[b_1 + \alpha b_2 - \alpha^2 b_3 - \cdots - \alpha^{m-1} b_m]. \tag{A2}
$$

Hypothesis (50) implies that $w > 0$.

We prove, exactly as in the proof of Theorem 2(b), that

$$
\dot{N} \le 0 \quad \text{when} \quad N = N^* + \varepsilon\frac{k}{\mu},
$$

$$
\dot{Y}_i \le 0 \quad \text{when} \quad Y_i = Y_i^* + \frac{\varepsilon}{\alpha^{m-i}},
$$

for $i = 3, \cdots, m$. For $i = 2$, on $Y_2 = Y_2^* + (\varepsilon/\alpha^{m-2})$,

$$\begin{aligned}
\dot{Y}_2 &= \frac{1}{b_1 D_1}\left[\frac{k}{c}V - (b_1 + kD_1 b_2)\left(Y_2^* + \frac{\varepsilon}{\alpha^{m-2}}\right)\right. \\
&\qquad \left. - kD_1 b_3 Y_3 - \cdots - kD_1 b_m Y_m\right] \\
&\le \frac{1}{b_1 D_1}\left[\frac{k}{c}(V^* + \varepsilon w) - (b_1 + kD_1 b_2)\left(Y_2^* + \frac{\varepsilon}{\alpha^{m-2}}\right)\right. \\
&\qquad \left. - kD_1 b_3\left(Y_3^* - \frac{\varepsilon}{\alpha^{m-3}}\right) - \cdots - kD_1 b_m\left(Y_m^* - \frac{\varepsilon}{\alpha^{m-m}}\right)\right] \\
&= 0 + \varepsilon\frac{kD_1}{b_1 D_1}\left[\frac{w}{cD_1} - \left(\frac{b_1}{\alpha} + b_2\right)\frac{1}{\alpha^{m-2}} + \frac{b_3}{\alpha^{m-3}} + \cdots + b_m\right] \\
&= 0,
\end{aligned}$$

by (46) and definition (A2) of w.

Finally, by (41), on $V = V^* + \varepsilon w$, $\dot{V}$ has the same sign as

$$\begin{aligned}
&(b_1 D_1 c - 1)N - (V^* + \varepsilon w) + D_1 c(b_2 - b_1)Y_2 + \cdots + D_1 c(b_m - b_1)Y_m \\
&\le (b_1 D_1 c - 1)\left(N^* + \varepsilon\frac{k}{\mu}\right) - (V^* + \varepsilon w) + D_1 c(b_2 - b_1)\left(Y_2^* \pm \frac{\varepsilon}{\alpha^{m-2}}\right) + \cdots \\
&\qquad + D_1 c(b_m - b_1)(Y_m^* \pm \varepsilon), \qquad \text{(A3)}
\end{aligned}$$

where we choose the plus sign in the $(Y_j^* + \varepsilon/\alpha^{m-j})$ term of (A3) if and only if $b_j - b_1 > 0$. Using $\dot{V}(X^*, \mathbf{Y}^*) = 0$, we conclude that (A3) equals

$$\begin{aligned}
&0 + \varepsilon\left[(b_1 D_1 c - 1)\frac{k}{\mu} - w + \frac{D_1 c}{\alpha^{m-2}}|b_2 - b_1| + \cdots + D_1 c|b_m - b_1|\right] \\
&= \varepsilon\frac{D_1 ck}{\mu}\left[\frac{b_1 D_1 c - 1}{D_1 c} - \frac{\mu}{k}\left(\frac{w}{D_1 c} - \frac{|b_2 - b_1|}{\alpha^{m-2}} - \cdots - |b_m - b_1|\right)\right] \\
&= \varepsilon\frac{D_1 ck}{\mu}\left[\frac{b_1 D_1 c - 1}{D_1 c} - \frac{\mu}{k\alpha^{m-1}}\left(b_1 + \alpha b_2 - \alpha^2 b_3 - \cdots - \alpha^{m-1} b_m\right.\right. \\
&\qquad \left.\left. - \alpha|b_2 - b_1| - \cdots - \alpha^{m-1}|b_m - b_1|\right)\right] \\
&\le 0, \qquad \text{by (50)}.
\end{aligned}$$

These calculations imply that the vector field points into B_ε of (A1) on the "upper" hypersurfaces of B_ε. Similar computations show that the vector field points into B_ε on the "lower" hypersurfaces, too. As in the proof of Theorem 2,

$$F(X, \mathbf{Y}) = \max\left\{\frac{\mu}{k}\|N - N^*\|,\ \frac{1}{w}\|V - V^*\|,\ \alpha^{m-2}\|Y_2 - Y_2^*\|, \cdots,\ \|Y_m - Y_m^*\|\right\}$$

is a global (piecewise smooth) Lyapunov function that guarantees the global stability of the endemic equilibrium.

To get some perspective on (50), we simplify its right-hand side in two special cases: (1) $b_1 \geq b_i$ for all i, and (2) $\beta_i = \beta$ for all i. In case (1), the right hand side of (50) simplifies to:

$$\begin{aligned}
&\frac{\mu(\mu+k)^{m-1}}{k^m}[b_1 + \alpha(2b_2 - b_1) - \alpha^2 b_1 - \cdots - \alpha^{m-1}b_1] \\
&= \frac{\mu(\mu+k)^{m-1}}{k^m}[b_1(1-\alpha-\alpha^2-\cdots-\alpha^{m-1}) + 2\alpha b_2] \\
&= \frac{\mu(\mu+k)^{m-1}}{k^m}\left[b_1\left(\frac{1-2\alpha+\alpha^m}{1-\alpha}\right) + 2\alpha b_2\right] \\
&= \left(\frac{\mu+k}{k}\right)^m [b_1(1-2\alpha+\alpha^m) + 2b_2\alpha(1-\alpha)].
\end{aligned}$$

It follows that (50) holds if $b_1 \geq b_i$ for all i and if

$$\text{(A4)} \qquad \frac{b_1 cD_1 - 1}{b_1 cD_1} \leq \left(\frac{\mu+k}{k}\right)^m \left[1 - 2\alpha + \alpha^m + \frac{2b_2}{b_1}\alpha(1-\alpha)\right].$$

If β_i is independent of i, then $b_1 \geq b_i$ for all i. In this case, $b_1 = (1-\alpha^m)\beta/(1-\alpha)$, $b_2 = (1-\alpha^{m-1})\beta/(1-\alpha)$, and (A4) becomes

$$\frac{b_1 cD_1 - 1}{b_1 cD_1} \leq \left(\frac{\mu+k}{k}\right)^m \frac{1 - 2\alpha^2 - 2\alpha^m + 4\alpha^{m+1} - \alpha^{2m}}{1-\alpha^m}.$$

Appendix B. Proofs of Theorems 5 and 6. We consider proportional mixing with deaths due to the disease, one infectious stage, and we assume the probability β of infection per contact with an infected person is the same for all population subgroups. Then, expression (51) becomes

$$\text{(B1)} \qquad \dot{V} = \left(\frac{\beta D \sum_j c_j^2 X_j}{\sum_j c_j N_j} - 1\right)\beta \sum_i c_i Y_i$$

THEOREM 5. *If* $\mathcal{R}_o - 1 = \left(\beta D \sum_j c_j^2 U_j\right)/\left(\sum_j c_j U_j\right) - 1 \leq 0$, *the disease-free equilibrium is globally asymptotically stable.*

Proof. Note that $\beta \sum_i c_i Y_i$ is always nonnegative but that $\mathcal{R} - 1$ can be positive or negative. Rearrange (B1) to give

$$\text{(B2)} \qquad \dot{V} = \left(\beta D \sum_j c_j^2 X_j - \sum_j c_j N_j\right)\frac{\beta \sum_j c_j Y_j}{\sum_j c_j N_j}.$$

Let

$$\text{(B3)} \qquad W \equiv \beta D \sum_i c_i^2 X_i - \sum_i c_i N_i,$$

so that W and $\dot{V}$ have the same sign in the interior of the region (6). By hypothesis,

$$\text{(B4)} \qquad \mu W(\mathbf{U}/\mu, \mathbf{0}) = \beta D \sum_i c_i^2 U_i - \sum_i c_i U_i \leq 0.$$

Now, $W = 0$ is a hyperplane that divides the positive orthant into two regions. The region containing the disease-free equilibrium has $W < 0$, the other region has $W > 0$. We show that $\dot{W} < 0$ on the half-space $W \geq 0$, so all trajectories move into a region where $W < 0$ and hence $\dot{V} < 0$.

Substituting for $\dot{X}_i$ and $\dot{N}_i$ in $\dot{W}$ gives (B5):

$$\begin{aligned}
\dot{W} &= \beta D \sum_i c_i^2 \Big(-c_i X_i \frac{\beta \sum_j c_j Y_j}{\sum_j c_j N_j} + U_i - \mu X_i\Big) - \sum_i c_i \Big(U_i - \mu N_i - k Y_i\Big) \\
&= -\beta^2 D \sum_i c_i^3 X_i \frac{\sum_j c_j Y_j}{\sum_j c_j N_j} + \beta D \sum_i c_i^2 U_i - \sum_i c_i U_i \\
&\qquad - \beta D \mu \sum_i c_i^2 X_i + \mu \sum_i c_i N_i + k \sum_i c_i Y_i \\
&= -\beta^2 D \sum_i c_i^3 X_i \frac{\sum_j c_j Y_j}{\sum_j c_j N_j} + \mu W\left(\frac{\mathbf{U}}{\mu}, \mathbf{0}\right) - \mu W(\mathbf{X}, \mathbf{Y}) + k \sum_j c_j Y_j \qquad \text{(B5)} \\
&= \left(k - \beta^2 D \frac{\sum_i c_i^3 X_i}{\sum_i c_i N_i}\right) \sum_j c_j Y_j + \mu \left(W\left(\frac{\mathbf{U}}{\mu}, \mathbf{0}\right) - W(\mathbf{X}, \mathbf{Y})\right).
\end{aligned}$$

Suppose that $W(\mathbf{X}, \mathbf{Y}) \geq 0$. Since $W(\mathbf{U}/\mu, \mathbf{0}) \leq 0$ and $k < k + \mu = 1/D$,

$$\begin{aligned}
\dot{W} &< \left(\frac{1}{D} \sum_i c_i N_i - \beta^2 D \sum_i c_i^3 X_i\right) \frac{\sum_i c_i Y_i}{\sum_i c_i N_i} \\
&\leq \Big(\sum_i c_i^2 \beta X_i - \beta^2 D \sum_i c_i^3 X_i\Big) \frac{\sum_i c_i Y_i}{\sum_i c_i N_i} \qquad \text{(since } W(X, Y) \geq 0\text{)} \\
&\leq \sum_j c_j^2 \beta X_j (1 - c_j D \beta) \frac{\sum_i c_i Y_i}{\sum_i c_i N_i} + \frac{\big(\sum_i c_i Y_i\big)^2}{D \sum_i c_i N_i} \qquad \text{(B6)} \\
&\leq \sum_j c_j^2 \beta X_j (1 - c_j D \beta) \frac{\sum_i c_i Y_i}{\sum_i c_i N_i} + \sum_j (c_j D \beta - 1) \frac{c_j X_j}{D} \frac{\sum_i c_i Y_i}{\sum_i c_i N_i} \\
&\quad \text{(since } W(X, Y) \geq 0\text{)} \\
&= \sum_j [D c_j^2 \beta X_j (1 - c_j D \beta) + (c_j D \beta - 1) c_j X_j] \frac{\sum_i c_i Y_i}{D \sum c_i N_i} \\
&= -\sum_j (c_j D \beta - 1)^2 c_j X_j \cdot \frac{\sum_i c_i Y_i}{D \sum c_i N_i} \\
&\leq 0.
\end{aligned}$$

Since $\dot{W} < 0$ when $W \geq 0$, orbits in the bounded region, $\{W \geq 0\}$ must eventually move into the $\{W < 0\}$ region; once in that region, they must stay in that region for all time. Therefore, for every orbit, $\dot{V}$ eventually becomes and remains negative, and the disease-free equilibrium is globally asymptotically stable.

Proof of Theorem 6. The proof of Theorem 6 for multiple stages is similar to the above proof of Theorem 5. We assume that β_{jr} depends only on the stage r and that

$$\hat{D}\bar{\beta} \equiv D \sum_{r=1}^{m} \beta_r (kD)^{r-1} \leq D \beta_m.$$

For $m > 1$,

$$W = \hat{D}\bar{\beta}\sum_i c_i^2 X_i - \sum_i c_i N_i \quad \text{and} \quad \dot{N}_i = U_i - \mu N_i - kY_{im}.$$

So, we rewrite (B5) as

$$\text{(B7)} \quad \dot{W} = -\bar{\beta}\hat{D}\sum_i c_i^3 X_i \frac{\sum_{jr} c_j \beta_r Y_{jr}}{\sum_j c_j N_j} + \mu W\left(\frac{\mathbf{U}}{\mu}, \mathbf{0}\right) - \mu W(\mathbf{X}, \mathbf{Y}) + k\sum_j c_j Y_{jm}$$

$$\leq -\bar{\beta}\hat{D}\sum_i c_i^3 X_i \frac{\beta_m \sum_j c_j Y_{jm}}{\sum_j c_j N_j} + k\sum_j c_j Y_{jm} \qquad \text{when } W(X,Y) \geq 0$$

$$< \sum_j c_j^2 \bar{\beta} X_j (1 - c_j \beta_m D)\frac{\hat{D}}{D}\frac{\sum_j c_j Y_{jm}}{\sum_j c_j N_j} + \frac{(\sum_j c_j Y_{jm})^2}{D\sum_j c_j N_j} \qquad \text{as in (B6)}$$

$$\leq \sum_j [\hat{D} c_j^2 \bar{\beta} X_j (1 - c_j \beta_m D) + (c_j \hat{D}\bar{\beta} - 1) c_j X_j] \cdot \frac{\sum_j c_j Y_{jm}}{D\sum_j c_j N_j}$$

$$\text{(B8)} \qquad = \sum_j c_j X_j [(1 - \beta_m c_j D)\hat{D} c_j \bar{\beta} + (c_j \hat{D}\bar{\beta} - 1)] \cdot \frac{\sum_j c_j Y_{jm}}{D\sum_j c_j N_j}.$$

If $\hat{D}\bar{\beta} \leq D\beta_m$, then the term in square brackets in (B8) is $\leq -(1 - \bar{\beta} c_j \hat{D})^2 \leq 0$ and $\dot{W} < 0$ when $W \geq 0$; and $\dot{V}$ is eventually negative on every orbit of the system.

Note that if $\bar{\beta}_j c_j \hat{D} < 1$ for all j, then all the coefficients of W are negative, and $\{W = 0\}$ does not intersect the interior of the positive orthant. Hence, if $W(\mathbf{U}/\mu, \mathbf{0}) \leq 0$, then W and $\dot{V}$ are negative throughout the positive quadrant; and the disease-free equilibrium is globally asymptotically stable.

Appendix C. Preferred mixing. The differential equations for preferred mixing with multiple stages of infection are

$$\text{(C1)} \quad \dot{X}_i = -\frac{c_i X_i r_i \sum_r \beta_{ir} Y_{ir}}{N_i} - c_i X_i (1 - r_i)\frac{\sum_j c_j (1 - r_j)\sum_r \beta_{jr} Y_{jr}}{\sum_j c_j (1 - r_j) N_j} + U_i - \mu X_i$$

$$\text{(C2)} \quad \dot{Y}_{i1} = +\frac{c_i X_i r_i \sum_r \beta_{ir} Y_{ir}}{N_i} + c_i X_i (1 - r_i)\frac{\sum_j c_j (1 - r_j)\sum_r \beta_{jr} Y_{jr}}{\sum_j c_j (1 - r_j) N_j} - (\mu + k) Y_{i1}$$

$$\text{(C3)} \quad \dot{Y}_{ir} = kY_{i,r-1} - (\mu + k) Y_{ir} \qquad \text{for } r = 2, \cdots, m,$$

for $i = 1, \cdots, n$. If V is the function defined in (64), then by substituting (C2) and (C3) for the $\dot{Y}_{is}$'s in $\dot{V}$, we compute

$$\dot{V} = \sum_i \frac{c_i (1 - r_i) D_1 b_{i1}}{1 - c_i r_i D_1 b_{i1}} \left(\frac{c_i X_i r_i \sum_r \beta_{ir} Y_{ir}}{N_i}\right)$$

$$+ \sum_i \frac{c_i^2 (1 - r_i)^2 D_1 b_{i1} X_i}{1 - c_i r_i D_1 b_{i1}} \left(\frac{\sum_j c_j (1 - r_j)\sum_r \beta_{jr} Y_{jr}}{\sum_j c_j (1 - r_j) N_j}\right)$$

$$- \sum_i \frac{c_i (1 - r_i)}{1 - c_i r_i D_1 b_{i1}} \left(\sum_r (b_{ir} - kD_1 b_{i,r+1}) Y_{ir}\right),$$

where $b_{i,m+1} = 0$. Applying the definition of b_{ir} in (24), we rewrite $\dot{V}$ as

$$\begin{aligned}\dot{V} &= \sum_i c_i(1-r_i)\sum_r \beta_{ir}Y_{ir}\left(\frac{D_1 b_{i1}c_i r_i X_i/N_i}{1-r_i c_i D_1 b_{i1}}\right)\\ &\quad + \sum_i c_i(1-r_i)\sum_r \beta_{ir}Y_{ir}\left(\frac{\displaystyle\sum_j \frac{c_j^2(1-r_j)^2 D_1 b_{j1}X_j}{1-c_j r_j D_1 b_{j1}}}{\sum_j c_j(1-r_j)N_j}\right)\\ &\quad - \sum_i \frac{c_i(1-r_i)\sum_r \beta_{ir}Y_{ir}}{1-c_i r_i D_1 b_{i1}}\\ &= \sum_i c_i(1-r_i)\sum_r \beta_{ir}Y_{ir}\left(\frac{\displaystyle\sum_j \frac{c_j^2(1-r_j)^2 D_1 b_{j1}X_j}{1-c_j r_j D_1 b_{j1}}}{\sum_j c_j(1-r_j)N_j}\right)\\ &\quad - \sum_i c_i(1-r_i)\sum_r \beta_{ir}Y_{ir}\left(\frac{1-r_i c_i D_1 b_{i1}X_i/N_i}{1-r_i c_i D_1 b_{i1}}\right) \qquad \text{(C4)}\\ &= \left(\frac{\displaystyle\sum_j \frac{c_j^2(1-r_j)^2 D_1 b_{j1}X_j}{1-c_j r_j D_1 b_{j1}}}{\sum_j c_j(1-r_j)N_j} - 1 - \frac{\displaystyle\sum_j \frac{c_j^2(1-r_j)r_j\bar{\beta}_j\hat{D}Y_j(\sum_r \beta_{jr}Y_{jr})/N_j}{1-c_j r_j\bar{\beta}_j\hat{D}}}{\sum_j c_j(1-r_j)\sum_r \beta_{jr}Y_{jr}}\right) \qquad \text{(C5)}\\ &\quad \times \left(\sum_i c_i(1-r_i)\sum_r \beta_{ir}Y_{ir}\right)\\ &= (\mathcal{R}-1-E)\,V^*,\end{aligned}$$

using the notation of (65)–(67). In transforming (C4) to (C5), we substitute $1-(Y_i/N_i)$ for X_i/N_i in (C4) and then simplify.

Finally, we need to show that the expression for E in (C5) and (67) is continuous at $\mathbf{Y} = \mathbf{0}$. Since $U_j/(\mu+k) \le N_j \le U_j/\mu$, we can consider E near $\mathbf{Y} = \mathbf{0}$ as the ratio (C6) of a quadratic function in the Y_{ir}'s with a linear function in the Y_{ir}'s

$$E \sim \frac{\sum a_{ijsr}Y_{ir}Y_{js}}{\sum \alpha_{jr}Y_{jr}}, \qquad \text{(C6)}$$

where the all the coefficients a_{ijsr} and α_{jr} are nonnegative and some are strictly positive. Use nm-dimensional spherical coordinates $(\rho, \phi_1, \cdots, \phi_N)$ in Y_{ir}-space to write the homogeneous function in (C6) as

$$E \sim \frac{\rho^2 A(\phi_1,\cdots,\phi_N)}{\rho B(\phi_1,\cdots,\phi_N)} = \rho\frac{A(\phi_1,\cdots,\phi_N)}{B(\phi_1,\cdots,\phi_N)}. \qquad \text{(C7)}$$

The linear function in the denominator of E in (67) is zero in the positive orthant only at $\mathbf{Y} = \mathbf{0}$. Therefore, the function B in (C7) is bounded away from zero in the positive orthant. This implies that the function in (C7) tends to 0 as $\rho \to 0$ and therefore that E is continuous at $\mathbf{Y} = \mathbf{0}$.

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REFERENCES

[1] R. M. ANDERSON AND R. M. MAY, *Population biology of infectious diseases: Part* I, Nature, 280 (1979), pp. 361–367.

[2] R. M. MAY AND R. M. ANDERSON, *Population biology of infectious diseases: Part* II, Nature, 280 (1979), pp. 455–461.

[3] R. M. MAY, R. M. ANDERSON, AND A. R. MCLEAN, *Possible demographic consequences of* HIV/AIDS *epidemics. I. Assuming* HIV *infection always leads to* AIDS, Math Biosci., 90 (1988), pp. 475–505.

[4] H. W. HETHCOTE, *Qualitative analysis of communicable disease models*, Math. Biosci., 28 (1976), pp. 335–356.

[5] A. LAJMANOVICH AND J. A. YORKE, *A deterministic model for gonorrhea in a nonhomogeneous population*, Math. Biosci., 28 (1976) pp. 221–236.

[6] H. W. HETHCOTE, *An immunization model for a heterogeneous population*, Theoret. Population. Biol., 14 (1976), pp. 338–349.

[7] H. R. THIEME, *Global asymptotic stability in epidemic models*, Springer–Verlag Lecture Notes in Math., 1017 (1983), pp. 608–615.

[8] ———, *Local stability in epidemic models for heterogeneous populations*, in Conference on Mathematics in Biology and Medicine, Bari, Italy, 1983, V. Capasso, E. Grosso, S. Paveri-Fontana, eds., Springer-Verlag, Lecture Notes in Biomath., 57, 1985.

[9] D. W. TUDOR, *An age dependent epidemic model with application to measles*, Math. Biosci. 73 (1985), pp. 131–147.

[10] H. W. HETHCOTE AND H. R. THIEME, *Stability of the endemic equilibrium in epidemic models with subpopulations*, Math. Biosci. 75 (1985), pp. 205–227.

[11] L. SATTENSPIEL AND C. P. SIMON, *The spread and persistence of infectious diseases in structured population*, Math. Biosci., 90 (1988), pp. 341–366.

[12] E. BERETTA AND V. CAPASSO, *On the general structure of epidemic systems. Global asymptotic stability*, Comput. Math. Appl., 12A (1986), pp. 677–694.

[13] ———, *Global stability results for a multigroup SIR epidemic model*, in Mathematical Ecology, T. Hallam, Gross, and S. Levin, eds., World Scientific, 1988.

[14] X. LIN AND J. W.-H. SO, *Global stability of the endemic equilibrium in epidemic models with subpopulations*, University of Alberta, preprint.

[15] J. A. JACQUEZ, C. P. SIMON, J. KOOPMAN, L. SATTENSPIEL, AND T. PERRY, *Modeling and analyzing* HIV *transmission: the effect of contact patterns*, Math. Biosci., 92 (1989), pp. 119–199.

[16] K. DIETZ, *Transmission and control of arbovirus diseases*, in Epidemiology: Proceedings of a SIMS Conference on Epidemiology, D. Ludwig and K. L. Cooke, eds., Society for Induatrial and Applied Mathematics, Philadelphia, PA, 1975, pp. 104–121.

[17] R. M. ANDERSON AND R. M. MAY, *Directly transmitted diseases: Control by vaccination*, Science, 215 (1982), pp. 1053–1060.

[18] K. DIETZ, *Mathematical models for infectious diseases—Evaluation of measures for prevention and control*, in Perspectives in Medical Statistics, J. F. Bithell and R. Coppi, eds., Academic Press, New York, 1981, pp. 65–84.

[19] H. W. HETHCOTE AND J. W. VAN ARK, *Epidemiological models for heterogeneous populations: proportionate mixing, parameter estimation, and immunization procedures*, Math. Biosci., 84 (1987), pp. 85–118.

[20] J. A. JACQUEZ, C. P. SIMON, AND J. S. KOOPMAN, *The reproduction number in deterministic models of contagious diseases*, Comm. Theoret. Biol., 2 (1991) pp. 159–209.

[21] X. LIN, *Qualitative analysis of an* HIV *transmission model*, Math. Biosci., 1991
[22] J. A. JACQUEZ, C.P. SIMON, AND J. KOOPMAN, *Structured mixing: Heterogeneous mixing by the definition of activity groups.* Mathematical and Statistical Approaches to AIDS Epidemiology, C. Castillo-Chavez, ed., Springer-Verlag, Lecture Notes in Biomath., 83 (1989) pp. 301–315.
[23] L. SATTENSPIEL, *Population structure and the spread of disease*, Human Biol., 59 (1987), pp. 411–438.
[24] V. ANDREASEN AND F. B. CHRISTIANSEN, *Persistence of an infectious disease in a subdivided population*, Math. Biosci., 96 (1989), pp. 239–253.
[25] T. YOSHIZAWA, *The Stability of Lyapunov's Second Method*, Tokyo Math. Soc. of Japan, Tokyo, 1966
[26] J. HALE, *Ordinary Differential Equations*, Krieger Publishing, Huntington, NY, 1980.
[27] W. HUANG, K. COOKE, AND C. CASTILLO–CHAVEZ, *Stability and bifurcation for a multiple group model for dynamics of* HIV/AIDS *transmission*, SIAM J. Appl. Math., 52 (1992), to appear.
[28] C. CASTILLO–CHAVEZ, K. COOKE, W. HUANG, AND S. LEVIN, *On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome* (AIDS). *Part* 2 : *Multiple group models*, in Mathematical and Statistical Approaches to AIDS Epidemiology, C. Castillo-Chavez, ed., Springer-Verlag, Lecture Notes in Biomath., 83 (1989), pp. 200–217.
[29] A. NOLD *Heterogeneity in disease–transmitting modeling*, Math. Biosci., 52 (1980), pp. 227–240.
[30] H. W. HETHCOTE, J. YORKE, AND A. NOLD, *Gonorrhea modeling: a comparison of control methods*, Math. Biosci., 58 (1982), pp. 93–109.