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A Risk-Based Heterosexual Model for the AIDS Epidemic with Biased Sexual Partner Selection

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INTRODUCTION

In this chapter we extend previous work on the spread of human immunodeficiency virus (HIV) in homosexual populations to study the spread of HIV infection in a purely heterosexual population. In this model the male and female populations are distributed continuously in risk. We study the impact of population structures and biases in sexual partner selection on the spread of the epidemic. As in the homosexual model, the epidemic is extremely sensitive to assumptions about sexual partner selection, as well as to the distribution of infectiousness over the duration of infection. Additionally, under strongly assortative mixing, waves of infection form and spread as in the homosexual model, although there tends to be significantly more cross-risk spread and wavefronts are broader than in the homosexual case. We show how the ratio of infections in male and female populations changes with different assumptions about male-to-female and female-to-male infectivity, and initial population distributions over risk.

Heterosexual contact is the primary mode of HIV transmission in many developing nations, accounting for the largest number of infections in Africa (1). Even in the United States, the fraction of AIDS cases attributable to heterosexual transmission is growing (2). The rate of spread appears to vary greatly from one region to the next, perhaps because of differences in health (including nutrition or other sexually transmitted diseases), sexual behavior, social structures, viral strains, or combinations of many factors.

Modeling studies have shown that the AIDS epidemic is sensitive to both the biological aspects of HIV infection and the human behaviors that spread HIV. Results from the simplest model vary greatly with the transmission probability, the

mean duration of infection, and the rate of new sexual (or needle-sharing) partner acquisition in the population. More sophisticated modeling studies have demonstrated that the epidemic is sensitive to more subtle features of the biology of HIV and of human behavior (3).

The acquisition of new sexual partners, which allows HIV to spread from person to person, is a complex social phenomenon, varying across cultures and between individuals, and over the life history of a given individual. The distribution of sexual partner acquisition rates within a population and the amount of mixing between behavioral levels has been found to be an important determinant of the rate and extent of spread of many sexually transmitted diseases. This was first demonstrated convincingly by the modeling work of Nold (4), Hethcote et al. (5), and Hethcote and Yorke (6), who found that structuring the promiscuous population into two activity levels was necessary to account for the spread of gonorrhea in a two-gender model, and that the amount of contact between the high- and low-risk groups was an important determinant of the spread. Anderson et al. (7) showed that the mean and the standard deviation of the partner-acquisition rate in the population are equally important determinants of the spread of HIV in homosexual populations. Hyman and Stanley (8,9) and Jacquez et al. (10) showed that both the assumed distribution of the population by partner-acquisition rates and the amount of mixing between groups with different rates greatly influence the spread of HIV in homosexual populations.

The biology of HIV infection is complex. The survival curve (the fraction of the population who have developed AIDS by duration of infection) is broadly distributed, with few people developing AIDS within the first 2 years after infection, and with a mean of approximately 10 years (11). A number of studies have demonstrated that models need to account adequately for the shape of this curve: either by assuming that the progression to AIDS occurs via a staged Markov process with five or more stages (10), or via a duration of infection variable (7).

HIV infectivity is another key determinant of the rate and extent of spread of the epidemic. In our earlier papers we showed that the manner in which infectivity varies with the course of the disease can greatly influence the pattern of spread of HIV, even when the mean infectiousness over the course of the disease is unchanged (8,9). In this chapter we show that the ratio between the male-to-female and female-to-male infectivities has a substantial, nonlinear impact on the male to female ratio of infection.

There is likewise substantial evidence that the infectiousness and susceptibility of people may be affected by the presence of cofactors, such as the presence of other cocirculating sexually transmitted diseases. Many researchers have speculated that infectiousness varies with the strain of HIV, which varies widely in genetic composition from one infected person to the next, and varies even more between regions and continents. However, although these are important factors in spreading the epidemic, we will neglect them in this model.

In this chapter we modify the homosexual model of Hyman and Stanley (8,9) to account for heterosexual HIV transmission, and use numerical simulations to study

its behavior. This model, which accounts only for spread between men and women by sexual contact, allows us to focus on questions related to sexual partner selection across risk levels and differences in infectivity between men and women. The model neglects transmission into this purely heterosexual subpopulation from people who have been infected through other means, such as intravenous drug use or sex between men. As in the homosexual case, we neglect age, migration, and many other important features of the epidemic.

In the next section we review the homosexual results and some preliminary results on the heterosexual model. Then we present the heterosexual transmission model, discuss our parameter estimates, and present the results from our computer simulations.

PREVIOUS RESULTS

In the homosexual model of Hyman and Stanley (8,9), the population is distributed according to their partner acquisition rate (which we will refer to as their *risk*), and divided into uninfected, infected-non-AIDS, and AIDS populations. The infected population is distributed further according to duration of infection, and AIDS cases are distributed according to duration of AIDS. There is a constant migration into and removal from the uninfected population, which creates a single equilibrium state in the absence of infection. The rate of infection of uninfecteds is determined by the rates of contact with infected people of a given duration of infection and partner acquisition rate (contacts with AIDS cases were neglected), multiplied by the infectivity of the partner. The rate of contact with infecteds depends on the rate of contact with people of a given risk, which can occur in a biased manner, and the fraction infected with that risk. Infected people develop AIDS at a rate that depends on their duration of infection, and people with AIDS die at a rate that depends on the duration of AIDS.

Using this model, we gained some interesting insights into the qualitative behavior of the AIDS epidemic (see also ref. 12), and showed that mixing is a crucial aspect of the spread. Random partner choice results in an exponentially growing epidemic. When the infected population, $I(t,r)$, is plotted against risk, r , at a given time, t , there is a single maximum in the infected population that remains at essentially the same risk value throughout the epidemic. This maximum in the infected population occurs at the same risk level as does the maximum value of $rN(0,r)$, where $N(0,r)$ is the initial population. This implies that, when partner selection is random, the most likely risk value for an infected person is the same as the most likely risk of a randomly chosen partner in the initial population. By contrast, self-selective mixing results in a polynomially growing epidemic that at first infects primarily high-risk people, and then sequentially moves into middle- and then low-risk populations.

Since the epidemic first spread into the higher risk populations, self-selective mixing results in an epidemic that is initially faster than random choice, but quickly

becomes slower after the infection saturates these high-risk groups. In fact, the initial epidemic grows exponentially under random mixing, and polynomially under self-selective mixing.

Variable infectivity during disease progression also has a strong influence on the growth rate of the epidemic. Changing the infectivity profile, while holding the average infectivity constant, results in different transient dynamics, but similar asymptotic states. Model results indicate that if there is a short burst of infectivity before the development of antibodies, it creates a rapid spread of the infection in populations that change partners on average once or more during the burst, but has little effect on populations that change partners much less frequently. Similarly, a long period of low infectiousness after infection delays the epidemic more in populations that change partners many times during this period than in those who change partners less frequently.

To extend our results to the spread of HIV in heterosexual populations and explore the impact of biased mixing, we need a continuous model of partner selection satisfying the heterosexual balance constraints. In Stanley et al. (13), we developed a model for this that we call the *low-risk rule*, and in Hyman and Stanley (14) and Stanley (15) we developed another model, the *asymmetric rule* [which is used in the iwgAIDS code (15)]. Castillo-Chavez and Busenberg (16) have developed a third heterosexual mixing model. Each of these three models uses an arbitrary function to set up desired mixing patterns.

In this chapter we compare the behavior of a heterosexual model using the low-risk and asymmetric rules. In Stanley et al. (13) and Hyman and Stanley (14) we presented some preliminary numerical explorations of this model, using the low-risk rule. Stanley (17) did numerical studies of the mixing that results from the asymmetric rule under various choices of population structures and mixing functions, finding that imbalances in the distribution of partners between male and female populations forces mixing across more risk levels than in homosexual populations. Kirschner (18) studied the behavior of this heterosexual HIV model with asymmetric mixing in the asymptotic limit of an infinitely narrow acceptance function, finding that this situation is quite different from the homosexual case. As we shall see, there are significant differences between homosexual and heterosexual spread.

A SIMPLE HETEROSEXUAL MODEL

Here we present the model of Hyman and Stanley (14). We consider a population in which the primary mode of HIV transmission is heterosexual sex, and all other modes can be neglected. We include in the modeled population all those who are at risk of infection via this route: This encompasses all people who have sex outside of mutually monogamous, lifetime relationships. The male and female at-risk populations are divided into uninfected people, those infected with HIV but who have not yet developed AIDS, and the infecteds who have progressed to AIDS. We assume

that the major factor affecting the probability of infection is the partner-acquisition rate and distribute each of these populations according to a risk variable that determines this rate. Non-AIDS infecteds also are distributed according to their duration of infection, and AIDS cases are distributed according to the duration of time since their diagnosis. People mature into a given risk group and leave it only when they become sexually inactive or die. Before the introduction of HIV, there was a balance between this constant maturation rate into each risk group and the constant rate per individual of retirement or death out of the population.

Uninfected people become infected through contacts with infected partners of the opposite sex. We assume that all contacts between individuals can be treated as events that occur at a single point in time (this assumption is discussed in more detail in the section on rate of infection). The transmission rate depends on the gender and duration of infection of the infected partner. Infected people develop AIDS at a rate that depends on the length of time they have been infected, but not on gender and risk. Persons with AIDS are assumed to be sexually inactive and to die at a rate that depends on the time since they were diagnosed. We thus model AIDS as a state in which most individuals have had a serious HIV-related illness, and have slowed or ceased sexual activity.

Unlike the homosexual model, the constraint that the number of partners be the same between the sexes (so that there is mathematically one male and one female member of each pair) implies that partner acquisition rates cannot remain fixed with time. Instead, pairing rates must be allowed to change as the relative sizes of the male and female populations, and their distributions over behavior, change. Therefore, we define a risk variable that measures the relative partner acquisition rates of two individuals of the same sex. For example, a woman with risk 10 will have twice as many partners per unit time as a woman with risk 5. The actual number of partners per year that is associated with a given risk level is then adjusted over time to ensure that the male/female pairings match.

Letting the subscript g refer to gender (M and F refer to males and females, respectively), we define

independent variables

- t time (years)
- τ duration of infection
- α duration of AIDS
- r risk
- τ_A time from infection to AIDS for a given individual

population sizes at time t , for risk r and gender g

- $U_g(t,r)$ uninfecteds, distributed by risk
- $I_g(t,r,\tau)$ non-AIDS infecteds, distributed by risk and duration of infection
- $A_g(t,r,\alpha)$ AIDS cases, distributed by risk and duration of AIDS
- $N_g(t,r)$ total number of sexually active individuals, distributed by risk:

$$N_g(t,r) = U_g(t,r) + \int_0^{\infty} I_g(t,r,\tau) d\tau$$

parameters

μ	per person rate of leaving the sexually active population
$U_{g0}(r)$	equilibrium distribution of the uninfected population of gender g over risk r in the absence of HIV
$i_g(\tau)$	probability of infection per contact with an infected person of gender g who has been infected τ years
$c_g(r, r')$	increased probability of transmission due to multiple contacts between a person of gender g and risk r with one of the opposite sex and risk r'
$\gamma_g(\tau)$	per person rate of developing AIDS for those of gender g infected τ years ago
$\delta_g(\alpha)$	per person death rate due to AIDS for those of gender g diagnosed α years ago
$f_g(r, s)$	function determining the mixing between a person of gender g , risk group r , and a person of the opposite gender, risk group s
$i_{gA}(\tau/\tau_A)$	infectivity at τ years after infection for a person of gender g who will develop AIDS τ_A years after infection
$N_{g0}(r)$	initial total population of gender g with risk r
$\langle r_g \rangle$	initial mean risk for gender g
$C_g(\tau)$	the fraction of the population of gender g developing AIDS by τ years after infection

functionals

$\lambda_g[t, r; U, I]$	per person rate of infection at time t for an uninfected person of gender g and risk r
$\pi_g[t, r; N]$	partner-acquisition rate at time t for a sexually active person of gender g and risk r
$\rho_g[t, r, s; N] ds$	probability at time t that the partner (of a person of gender g and risk r) has risk in the risk interval $(s, s + ds)$
$R_g[t; N]$	factor determining the partner-acquisition rates for a given gender at time t

The risk variable r is assumed to be proportional to the partner-acquisition rate, and continuously distributed. We assume that if male and female populations were identical, r would in fact be the partner-acquisition rate: however, as we show below, the constant of proportionality between r and the partner-acquisition rate must vary as the male and female populations change. Since partner-acquisition rates do not have a fixed upper bound, in our model we allow risk to range from zero to infinity. Likewise, we do not place an upper bound on the duration of infection and the duration of AIDS, although for the purposes of numerical simulations, we place a bound on each of these three variables.

Note that, since risk has the units partners/time, the distributions $U_g(t, r)$ and $U_{g0}(r)$ have the units people-time/partners and the distributions $I_g(t, r, \tau)$ and $A_g(t, r, \alpha)$ have the units people/partners.

Based on our assumptions, we have the following equations for the changes in the populations of gender g , risk r , at time t :

$$\begin{aligned}
\frac{\partial U_g(t,r)}{\partial t} &= \mu(U_{g0}(r) - U_g(t,r)) - \lambda_g[t,r;U,I]U_g(t,r), \\
I_g(t,r,0) &= \lambda_g[t,r;U,I]U_g(t,r), \\
\frac{\partial I_g(t,r,\tau)}{\partial t} + \frac{\partial I_g(t,r,\tau)}{\partial \tau} &= -(\gamma_g(\tau) + \mu)I_g(t,r,\tau), \\
A_g(t,r,0) &= \int_0^\infty \gamma_g(\tau)I_g(t,r,\tau)d\tau, \\
\frac{\partial A_g(t,r,\alpha)}{\partial t} + \frac{\partial A_g(t,r,\alpha)}{\partial \alpha} &= -(\delta_g(\alpha) + \mu)A_g(t,r,\alpha).
\end{aligned} \tag{1}$$

The first of these equations states that the rate of change of the uninfected population of gender g equals the rate at which people enter the population, $\mu U_{g0}(r)$, minus the rate at which they leave and the rate at which they are infected. The first two terms in this equation ensure that, in the absence of infection, the equilibrium uninfected population is $U_{g0}(r)$. The second equation states that infection occurs at $\tau=0$, and the number of new infections at time t is equal to the rate of infection of uninfecteds. The left-hand side of the third equation ensures that the duration of infection increases continuously and uniformly with time, and the right-hand side gives the departures from the infected population caused by the development of AIDS and out-migration. Similarly, AIDS occurs at $\alpha=0$ (fourth equation), and duration of AIDS increases uniformly in time (fifth equation).

Rate of Infection

The above model assumes a per-partner probability of transmission. Since we assume that the risk of infection from each new partner occurs instantaneously, the rate of infection, $\lambda_g[t,r;U,I]$, is a product of the partner acquisition rates, $\pi_g[t,r;N]$, and the probability of infection per partner. The probability of infection from a new partner depends on the risk level of the partner, which is determined by $\rho_g[t,r,s;N]$, and the probability of infection by a partner from that risk group, integrated over all possible risk groups of the partner:

$$\lambda_g[t,r;U,I] = \pi_g[t,r;N] \int_0^\infty \rho_g[t,r,x;N] k_g[t,r,x;U,I] dx. \tag{2}$$

Here $k_g[t,r,x;U,I]$ is the probability that a person of gender g , risk r , will be infected at time t , given that he/she has a partner of risk x , whose infection status is unknown:

$$k_g[t,r,x;U,I] = c_g(r,x) \int_0^\infty i_j(\tau) \frac{I_j(t,x,\tau)}{N_j(t,x)} d\tau, j \neq g. \tag{3}$$

The ratio $I_j(t,x,\tau)/N_j(t,x)$ is the probability that a person of gender j and risk x is infected for a time τ , and $c_g(r,x)i_j(\tau)$ is the probability of infection transfer to an uninfected person of gender g and risk r given that he/she has a contact with a person of gender j and risk x who has been infected for a time τ . We account for

increased transmission due to multiple contacts within a single relationship by multiplying the probability of transmission due to a single contact by a factor $c_g(r, x)$. Note that the factor $c_g(r, x)$ accounts only for increased transmission, and does not account for some of the other features of long-term relationships, such as overlap with other relationships. Note also that we do not account for increased susceptibility and infectivity due to the increased prevalence of other sexually transmitted diseases in higher risk individuals, although the factor $c_g(r, s)$ could be used indirectly to do this.

Partner-Acquisition Rates

Because each heterosexual pair involves a man and a woman, the total number of female partners that men have per year equals the number of male partners that women have per year. As populations change in size and structure, this balance has to be maintained in our mathematical model, which is equivalent to requiring that

$$\int_0^{\infty} \pi_M[t, r; N] N_M(t, r) dr = \int_0^{\infty} \pi_F[t, r; N] N_F(t, r) dr. \quad [4]$$

The population structures in our model will change over time. We expect not only that people with high values of r will be more likely to be infected sooner, but also that the two sexes will be affected differently by the disease. The behavior in a population will change as the epidemic proceeds, depending on its social structure and the way in which the people in it view the epidemic. In this model, we do not account for changes in risk of people who are already in the population, but we still need to adjust the partner-acquisition rates in a manner that ensures that Equation [4] holds at all times. We adjust the partner-acquisition rates by assuming that lower risk people will change less in absolute numbers than higher risk people (going from one partner per year to two is a bigger change than going from 50 to 51), and that partner-acquisition rates are proportional to risk. This allows us to use a time-dependent scaling factor, $R_g[t; N]$, which adjusts the partner-acquisition rates for each gender:

$$\pi_g[t, r; N] = R_g[t; N] r, \text{ for } g \in \{M, F\}. \quad [5]$$

The rescaling factor could be chosen in any way that would satisfy Equation [4], although the partner-acquisition rates of each population should go to zero if the other population vanishes. Indeed, there are many different ways that $R_g[t; N]$ could be chosen (see ref. 19), and Le Pont and Blower (20) have shown that the manner in which the adjustment occurs is important to the calculated spread of HIV. Unfortunately, there is little information on the manner in which populations actually do adjust casual sex partner selection. We assume that neither sex dominates, so that the rescaling is symmetric. We keep the scaling mathematically simple by choosing $R_g[t; N]$ so that the total number of sex partners for each gender is equal to the geometric mean of the total risks of men and women (where the total risk is $\int_0^{\infty} r N_g(t, r) dr$):

$$R_g[t; N] = \left[\int_0^{\infty} r N_f(t, r) dr \right]^{1/2} \left[\int_0^{\infty} r N_g(t, r) dr \right]^{-1/2}, \text{ for } g \neq j, \quad [6]$$

to ensure that Equation [4] holds at all times.

Partner Selection

We next need to specify a model of partner selection across risk groups. Given that the total number of partners balance, there are constraints on $\rho_g[t, r, s; N] ds$, the probability at time t that the partner (of a person of gender g and risk r) has a risk value in the interval $(s, s + ds)$. These are

$$\int_0^\infty \rho_g[t, r, s; N] ds = 1, \quad g \in \{M, F\}, \quad [7]$$

and

$$\rho_M[t, r, s; N] \pi_M[t, r; N] N_M(t, r) = \rho_F[t, s, r; N] \pi_F[t, s; N] N_F(t, s). \quad [8]$$

The first constraint states that when a partner is chosen they have some risk value, s . Equation [8] is the balancing condition ensuring that the number of partners that men of risk r have from the group of women of risk s is the same as the number that women of risk s have from the group of men of risk r .

Many alternative models could be used to specify the mixing functions. We explore two possibilities. Each model relies on *acceptance* functions for each gender $f_g(r, s)$, to determine who is paired with whom. These acceptance functions must be nonnegative, but otherwise are arbitrary.

In the *low-risk rule* (13,14), those of lowest risk in both sexes pick first and entirely determine what happens to those of higher risk:

For $r < s$:

$$\rho_g[t, r, s; N] = \left(1 - \int_0^r \rho_g[t, r, x; N] dx\right) \frac{f_g(r, s) \pi_j[t, s; N] N_j(t, s)}{\int_0^\infty f_g(r, x) \pi_j[t, x; N] N_j(t, x) dx} \quad [9]$$

For $r > s$:

$$\rho_j[t, r, s; N] = \frac{\rho_g[t, s, r; N] \pi_g[t, s; N] N_g(t, s)}{\pi_j[t, r; N] N_j(t, r)}, \quad \text{for } g \neq j \in \{M, F\}. \quad [10]$$

The *asymmetric rule* [see Hyman and Stanley (14) and Stanley (15,17)] is based on the idea that one sex does all of the choosing, with low-risk individuals choosing first. Letting the choosing sex be denoted by a superscript g :

$$\rho_g^g[t, r, s; N] = \frac{\left(1 - \int_0^r \rho_j^g[t, s, x; N] dx\right) f_g(r, s) \pi_j[t, s; N] N_j(t, s)}{\int_0^\infty f_g(r, y) \left(1 - \int_0^y \rho_j^g[t, y, x; N] dx\right) \pi_j[t, y; N] N_j(t, y) dy}, \quad [11]$$

$$\rho_j^g[t, r, s; N] = \rho_g^g[t, s, r; N] \frac{\pi_g[t, s; N] N_g(t, s)}{\pi_j[t, r; N] N_j(t, r)}, \quad \text{for } g \neq j \in \{M, F\}. \quad [12]$$

Using this idea, we can create mixing functions using female-choice, male-choice, or a linear combination of the two. In particular, a symmetric mixing function is obtained by averaging the rules for the two sexes:

$$\rho_g^{avg}[t, r, s; N] = \frac{1}{2} \left\{ \rho_g^M[t, r, s; N] + \rho_g^F[t, r, s; N] \right\}, \quad \text{for } g \in \{M, F\}. \quad [13]$$

Although the low-risk rule satisfies the constraints in Equation [7], the resulting partnership distribution, $\rho_R[t, r, s; N]$, may be discontinuous across the line $r = s$ because of the discontinuity in definition between Equations [9] and [10]. It is more difficult to see that the asymmetric rule also satisfies the integral constraints on the ρ_R (see ref. 15), and experience has shown that numerical convergence is very slow unless we restrict ourselves to functions $f_R(r, s)$ that converge to a function of r alone as r becomes large. This is equivalent to requiring that people at high risk must choose their partners randomly from the available pool, after the low-risk people have chosen [for both rules choosing an acceptance function that is independent of the partner's risk, i.e. $f_R(r, s) = f(r)$, gives random mixing]. Despite these difficulties, we can study a variety of mixing patterns by varying the functions $f_R(r, s)$.

Equations [5] and [6] specify the partner-acquisition rates for each individual in the population. It may be, as the two companion papers by Jacquez et al. (10) and Koopman et al. (21) argue, that it is sociologically unrealistic to fix the partner-change rate. However, a formulation that can allow us to impose specified partner-change rates does have the advantage that we can match current data on partner-change rates.

In the next section we give parameter specifications for this model. We need to specify the initial conditions and immigration rates for each sex, the mixing behavior, the number of contacts per partner, the infectivity per contact in each direction, the conversion-to-AIDS rates, and the death rates.

MODEL PARAMETERS

Duration of Infection and Death Rates

We assume that the rate of developing AIDS and the death rate from AIDS are the same for both genders, although there is some evidence that they may be significantly different (22). We assume the Weibull distribution of Medley et al. (23), so that the probability that a person of gender g develops AIDS τ years after infection is

$$\frac{dC_g(\tau)}{d\tau} = pq^p \tau^{p-1} e^{-(q\tau)^p}, \quad [14]$$

with $p = 2.4$ and $q = 0.11$. The term $C_g(\tau) = 1 - e^{-(q\tau)^p}$ is the fraction developing AIDS by τ years after infection. The mean time to AIDS for this distribution is 8 years. The rate of developing AIDS is given by

$$\gamma_g(\tau) = \frac{C'_g(\tau)}{1 - C_g(\tau)} = pq^p \tau^{p-1}, \quad g \in \{M, F\}, \quad [15]$$

where the prime denotes differentiation. We assume that the AIDS death rate is

$$\delta_g(\alpha) = D'(\alpha)/(1 - D(\alpha)), \quad g \in \{M, F\}, \quad [16]$$

where

$$\frac{dD(\alpha)}{d\alpha} = \exp\left\{\frac{-0.75\alpha}{1+0.05\alpha}\right\} \int_0^{\infty} \exp\left\{\frac{-0.75x}{1+0.05x}\right\} dx \quad [17]$$

is the probability density of dying from AIDS α years following the development of AIDS. This function was estimated from Centers for Disease Control (CDC) data (see ref. 8). Finally, we fix the natural death rate for both sexes at

$$\mu_g = 0.02 \text{ years}^{-1}, \quad g \in \{M, F\}, \quad [18]$$

so that the mean amount of time spent in the at-risk, sexually active population is assumed to be 50 years for both sexes in the absence of AIDS.

Infectiousness

It has been speculated that infected persons may have a burst of viremia just before the development of antibodies (on average about 6 weeks after infection), usually are not very infectious for many years, and then gradually become more infectious as their immune systems begin to break down (11,24), either because of a varying viral burden (25) or because of a more aggressive viral strain that dominates toward the end of infection (26). A number of partner studies have found a correlation between transmission and either low CD4 helper cell counts or disease symptoms in the originally infected partner (27,28). Circumstantial evidence for this pattern of infectiousness also comes from studies of pregnant women (which cannot be used as direct evidence because perinatal transmission is a different route than sexual transmission). The hypothesis of an early burst of infectiousness is supported by studies that have found that pregnant women are more likely to infect their fetus when they become infected during pregnancy. Studies finding that women also are more likely to infect their fetus when they begin to have a positive P24 antigen test, indicating higher viral activity and/or lower CD4 numbers (29), provide support for the idea that infectiousness increases as the immune system deteriorates, although a recent paper that examined cell-free cervical secretions from women found no correlation between a positive culture and disease stage (30).

In Equations [8] and [9] we showed that strong variations in infectiousness with disease stage can change the epidemic substantially. To study the potential impact of disease-linked infectiousness, we make the simple assumption that disease stages progress at a linear rate with respect to time to AIDS: a person who develops AIDS twice as fast spends half as much time in each disease stage. Thus, we assume that an individual of gender g who develops AIDS τ_A time units after infection has an infectivity $i_{gA}(\tau/\tau_A)$ at τ time units after infection. In the appendix we show that this assumption gives an average infectivity $i_g(\tau)$ of the people of gender g infected for τ units of time:

$$i_g(\tau) = [1 - C_g(\tau)]^{-1} \int_0^{\infty} i_{gA}(\tau/\tau_A) \frac{dC_g(\tau_A)}{d\tau_A} d\tau_A, \quad g \in \{M, F\}. \quad [19]$$

In all of the simulations reported below we set

$$i_{gA}(x) = \beta_g i_L(x), \quad [20]$$

where $i_L(x)$ is a piecewise linear function connecting the points $\{(0,0), (0.013,0), (0.05,1), (0.088,0.4), (0.625,0.4), (1,1)\}$. Thus, we have assumed that there is a sharp peak in infectiousness shortly after infection, followed by a long noninfectious period, and then a rise shortly before the start of AIDS. This gives a mean value for $i_g(\tau)$ of $0.06\beta_g$. These points are chosen so that a person who takes 8 years to develop AIDS spends 0.1 years before becoming infectious, reaches maximum infectiousness 0.4 years after infection, reaches the low infectious period 6 months after infection, and then begins to become infectious again 5 years after infection. A plot of the function $i(\tau)$ that results from this is given in ref. 8.

If male partners are much less likely to become infected than female partners, this will affect the rates and pattern of spread of the epidemic. Most studies of couples have found that this is true (31), although it is not clear how much larger $i_M(\tau)$ is than $i_F(\tau)$ [in ref. 32, 1% of women and 20% of men have infected their partners, whereas in the European Partner Study (28) 12% of women and 20% of men infected their partners]. One theory proposed to explain the large female-to-male ratio of heterosexual infections is that it is caused entirely by this difference in transmission. We will explore this through different choices of the multipliers, β_g , in our simulations.

Data on transmission indicate that multiple contacts with an infected person may increase the probability of transmission (27,28). In studies of high-risk populations, in which only a few contacts per partner are likely, transmission probabilities per partner are on the order of a few per thousand (33). In contrast, the probability of being infected through a large number of contacts with the same infected partner (in studies with more than 20 couples) has ranged from 1% to 73% (27,28,31,32,34,35).

On the other hand, in a number of cohort studies, the probability that both partners are infected does not seem to be correlated with the number of contacts since the first partner was infected (24,34). In some studies infection transfer is not occurring in continuing relationships (e.g., refs. 36,37), whereas in others it is (38). This may be because of the variable infectivity profile: a randomly chosen partner is unlikely to be in the early viremic stage, whereas a contact during this stage with a long-term partner who becomes infected during the relationship is likely. It also may be that some people are never very infectious, either because of their own good health or the strain of virus they carry, or that some people are not very susceptible to infection for unknown reasons.

We modulate the infectivity by the contact function, which is intended to account for the increase in transmission with duration of the relationship. To keep this simple, in all but one simulation we use the following function for $c_g(r,s)$, the increased probability of transmission due to multiple contacts between a person of gender g and risk r with one of the opposite sex of risk s :

$$c_g(r,s) = c_f(s,r) = 1 + 19e^{-0.05(r+s)}. \quad [21]$$

This function is chosen so that the probability of transmission in a long-term relationship (assuming that a relationship between men and women who both have risk 0 will be long-term) is 20 times that of a very short-term relationship (assuming that a relationship between men and women who have high risk will be short). This is intended to be consistent with the estimates given above, without overestimating the impact of multiple contacts. We investigate the sensitivity of our results to this decay (in the section on contacts per partner) by comparing the baseline scenario with the case where c_g is constant.

Initial Population Distributions

Many sexual behavior surveys [see, e.g., refs. 39–42 and the AIDS in Multiethnic Neighborhoods (AMEN) survey (43)] have been conducted over the past 10 years. Although most of these studies have flaws (such as being of nonrepresentative populations), they do yield some information about the distribution of populations by partner acquisition rates. One of the best surveys conducted in the United States is the AMEN study (43), which used a random household-based design to select participants from selected census tracts in San Francisco. We have analyzed data from this study to obtain reasonable distributions of the population over risk.

In the AMEN study, men who had ever had sex with a woman were asked their number of partners in the past 10 years and in the past 1 year. A group of 747 men reported having sex with women in the past 10 years. This group reported a mean of 2.4 female partners in the past year, with the most active man reporting 130 female partners. We have estimated the distribution, $\theta(p)$, of these men over the number of partners per year, p , by first calculating the cumulative sum to obtain the fraction, $\Theta(p)$, of the men with less than or equal to p partners in the past year, and then approximating the derivative of that fraction. The 747 men each reported one of 20 different values of p . Letting these 20 values be denoted by p_j , for $j=1,2,\dots,20$, $\Theta(p)$ jumps at each of these 20 values. In Fig. 1 we used centered differences to estimate $\theta(p)$ halfway between each pair of data points as

$$\theta\left(\frac{p_j + p_{j+1}}{2}\right) = \frac{\Theta(p_{j+1}) - \Theta(p_j)}{p_{j+1} - p_j}. \quad [22]$$

In our simulations, we assume that the initial population distribution of both sexes decays according to r^{-n} for large risk, for some number n :

$$N_{g0}(r) = \frac{N_{gT}(n_g - 1)}{2a_g} \frac{(1 + (n_g + 1)r/a_g)}{(1 + r/a_g)^{n_g + 1}}. \quad [23]$$

Here N_{gT} is the total population of gender g . The parameters n_g and a_g determine the mean risk and decay rate with increasing risk. For this distribution, the initial mean risk for gender g , which we denote by $\langle r_g \rangle$, is

$$\langle r_g \rangle \equiv \int_0^\infty r N_{g0}(r) dr \left[\int_0^\infty N_{g0}(r) dr \right]^{-1} = \frac{3a_g}{2(n_g - 2)}. \quad [24]$$

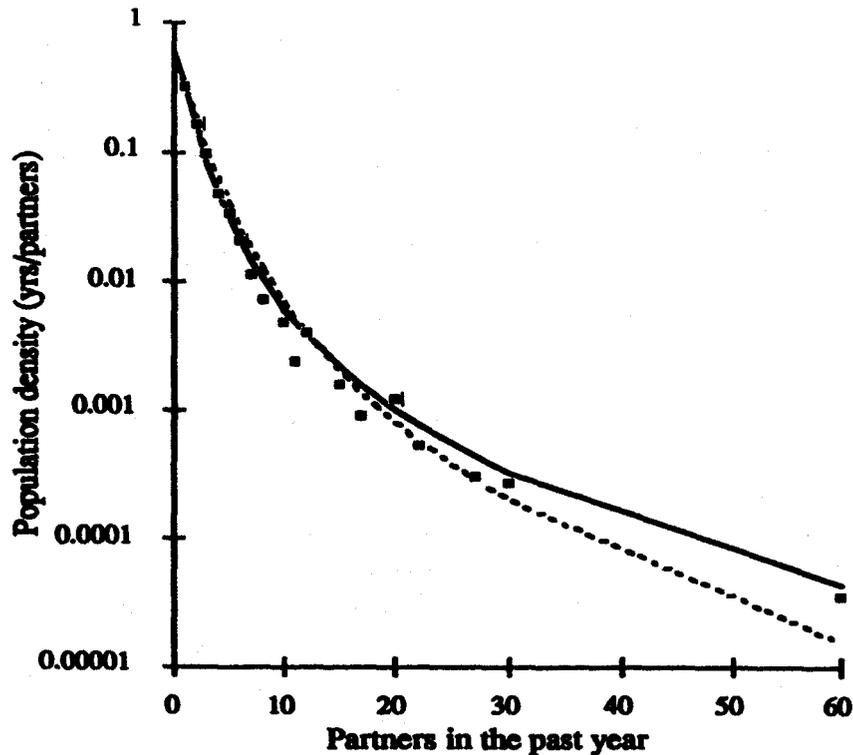


FIG. 1. The distribution of the population by risk for the AMEN study. Dots indicate the points calculated from the data, as explained in the text. The curves were calculated from Equations [23] and [24], with $a_M = 2(n_M - 2) \langle r_M \rangle / 3$, where $\langle r_M \rangle$ is the data mean of 2.4 partners/yr. Solid line is the inverse cubic ($n_M = 3$), dashed line the inverse quartic ($n_M = 4$).

In Fig. 1 we compare θ from the data to our assumed distribution, $N_{MO}(r)/n_{MT}$, obtained by taking the mean to be 2.4 partners/year and using Equations [23] and [24] to define $N_{MO}(r)$. We consider the cases $n_r = 3$ and $n_r = 4$. This distribution function is a reasonably good fit to the data, with n_r somewhere between 3 and 4, although the fitted functions both predict that a little more of the population would lie between 7 and 20 partners per year than is seen in the data. Note that there are some real difficulties involved in fitting the data: for one thing, the scatter in the data at high partner numbers and the large intervals between data points imply that the derivative estimates are difficult to interpret there; for another we have treated the number of female partners in the past year in this data set as if it were the number of new partners in the past year, and a lifetime habit. This is clearly not the case. Further work to differentiate the number of partners and the partner-acquisition rate would give a much better sense of the actual distribution function. We have noted as well only that the distributions are similar: we have not calculated the goodness of fit.

Equation [4] implies that when male and female populations are the same size, they must have the same mean partner-acquisition rates. However, population-

based surveys usually find that the number of nonmonogamous women and their mean number of male partners is lower than for the men surveyed. For example, in a 1987 telephone survey in California of 839 men and 1,173 women, 14% of men but only 5% of women responded that they had two or more partners of the opposite sex in the past year, with a mean of five and three partners for the men and women, respectively, with multiple partners (41). This apparent imbalance cannot be explained by the idea that there are more sexually active women than men, since more women (25%) reported no sex partners of the opposite sex in the past year than men (13%), and the fractions of women and men reporting one partner were roughly equal (68% and 71%). Obviously, it is possible either that men are exaggerating and women are underestimating their number of partners, or both. Another possibility is that an important group of women is missed by surveys. This group may include very young women, who are below the cutoff age for the survey (age 18 in ref. 41), but it also may include highly active women, many of whom may not be part of mainstream society. If there is a small subgroup of highly active women, then the distributions of men and women over partner-acquisition rates are shaped differently, even though their means are similar. For example, if we believe Equation [24] for both men and women, then it may be that $n_M > n_F$.

In our simulations, we examine the sensitivity of the model to the shape of the distributions of males and females defined by Equations [23] and [24]. We choose the parameters so that males and females have an initial mean risk of 3, and take the total initial population size to be $N_{rT} = 1$. Note that since mean risks between men and women are balanced at the start of each calculation, and population sizes are the same, the initial partner-acquisition rate is equal to the risk variable.

We found, in the homosexual case, that the spread of infection was fairly insensitive to the risk distribution of the initial infected population, so we take the initial distributions of infecteds and AIDS cases to be uniform in risk, and modulated by a presumed distribution over duration of infection or AIDS. This presumed distribution assumes polynomial growth in infection over time before the start of the calculation, and keeps the τ - and α -dependence smooth at the start of the simulations:

$$I_r(0, r, \tau) = \begin{cases} 3 \times 10^{-6} (10 - \tau)^2, & \text{for } \tau < 10 \\ 0, & \text{for } \tau \geq 10 \end{cases} \quad [25]$$

$$A_r(0, r, \alpha) = (0.1) I_r(0, r, \alpha), \quad \text{for all } \alpha.$$

The initial susceptible population is then

$$U_r(0, r) = N_{r0}(r) - I_r(0, r) - A_r(0, r), \quad g \in \{M, F\}, \quad [26]$$

where $I_r(t, r)$ is the integral over all τ of $I_r(t, r, \tau)$ and $A_r(t, r)$ is the integral over all α of $A_r(t, r, \alpha)$. We take the immigration to be such that the equilibrium population in the absence of HIV is $N_{r0}(r)$:

$$U_{r0}(r) = N_{r0}(r) \quad [27]$$

Mixing

Who mixes with whom is determined by the acceptance functions and mixing algorithm. For the mixing functions, we assume that people prefer to choose partners who are similar to themselves, and let

$$f_g(r,s) = \left[1 + 100 \left(\frac{r-s}{r+4} \right)^3 \right]^{-1}, \quad g \in \{M, F\}. \quad [28]$$

Unless otherwise specified, we use the asymmetric mixing formulation with female choice and the mixing function of Equation [28] in the calculations that follow. Figure 2 shows the mixing functions for this case when both male and female population distributions are given by Equation [23], with $n_r = 3$ and $a_r = 2$. Even though both populations are identical, on average females of moderate risk pair with males of slightly lower risk than themselves. The reasons for this are seen in the male mixing function of Fig. 2B: a large fraction of moderate and high-risk men are paired with low-risk women. This occurs because the population distribution drops rapidly with risk, and women of very low risk occasionally pair with men at higher risk than themselves: their large numbers imply that they use up many of the partner slots available to the small numbers of high-risk men, and women at mid- to high risk end up pairing with men of lower risk than themselves. This mixing thus ends up being broader than in the homosexual case with the same mixing function (see ref. 9).

Below (in the section on mixing rule) we examine the sensitivity of the model to the choice of mixing rule. Figure 3 shows the initial mixing for these different rules. Note that male choice in the asymmetric rule would simply reverse the labels on Fig. 2 (given that the male and female populations are identically distributed), and thus is not shown. Averaging male and female choice gives the average of Figs. 2A and 2B for both males and females. Although this seems intuitively more realistic than either male or female choice, when implemented mathematically it results in an odd-looking multiple-humped mixing function, with broad mixing across risk levels. The low-risk rule gives biased mixing when the populations are identical. The discontinuities are the result of the discontinuity between the two equations ([9] and [10]) that define the low-risk rule model.

SAMPLE CALCULATIONS

All calculations were run using a uniform grid in the r and τ directions with a 100×40 grid. The maximum risk was 50 partners per year and the maximum τ was 20 years. For the cases in which men and women were distributed differently in risk, the initial risk had to be adjusted using Equation [4] to ensure balancing, because of endpoint effects. The integrals were calculated using a trapezoidal rule, and an Adams-Bashford-Moulton variable time-step method [from the SDRIV code (44)] was used in time to maintain the error tolerance below 10^{-6} per unit time.

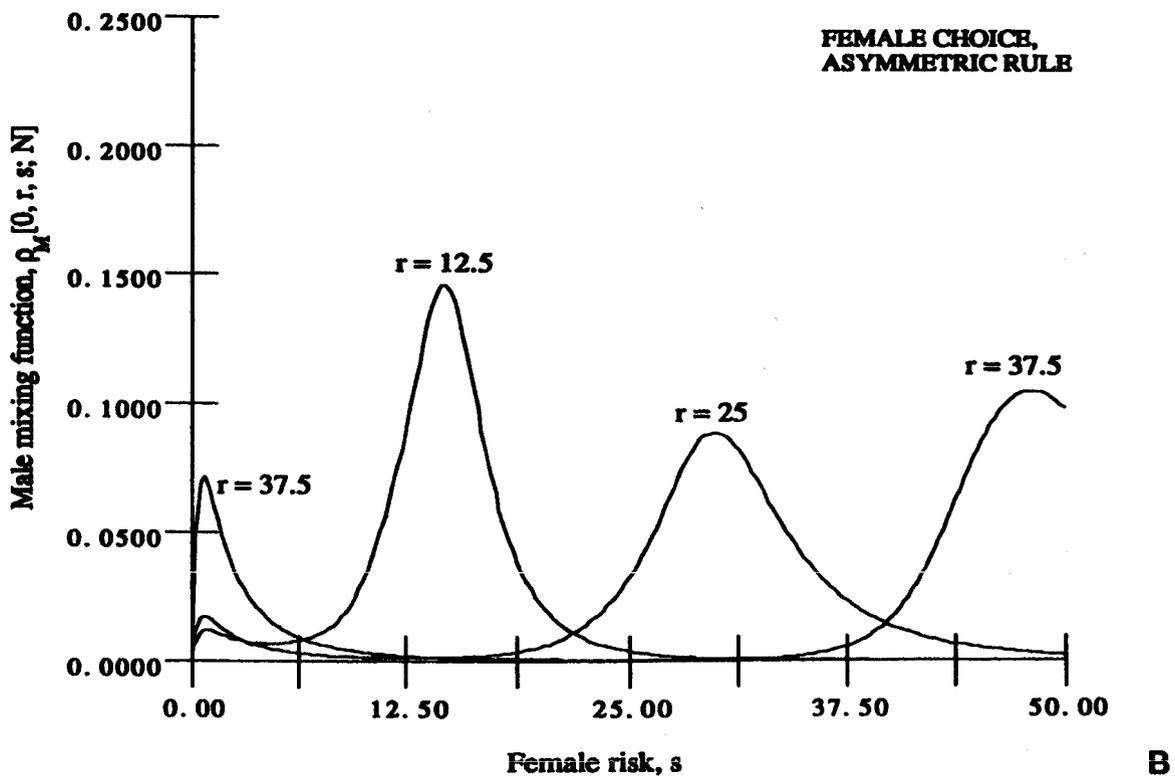
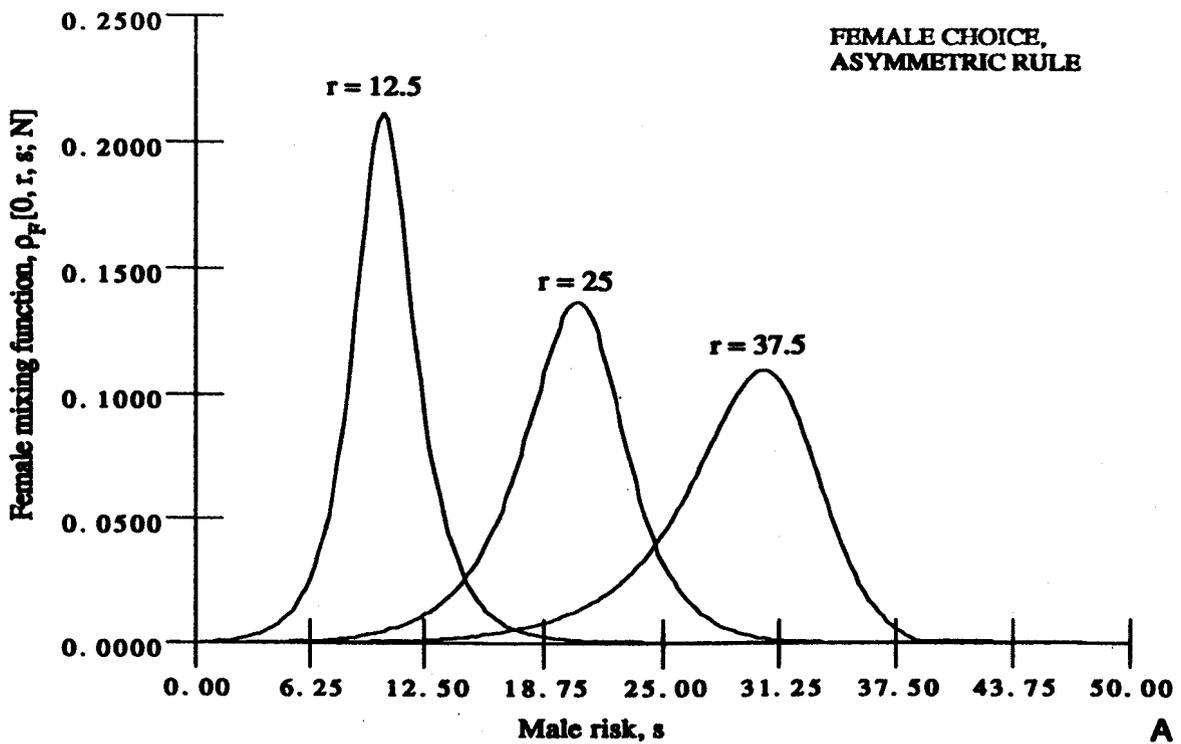


FIG. 2. The mixing functions obtained by assuming female choice and using the asymmetric mixing rule. **A:** The distribution of male partners of women. Here r indicates the woman's risk, and the distribution is given for women of risk 12.5, 25, and 37.5. **B:** The distribution of female partners of men, for men of risk 12.5, 25, and 37.5. The population distributions for males and females are both given by Equations [23] and [24], with $n_o = 1$ and $a_o = 2$. The acceptance function is given by Equation [28].

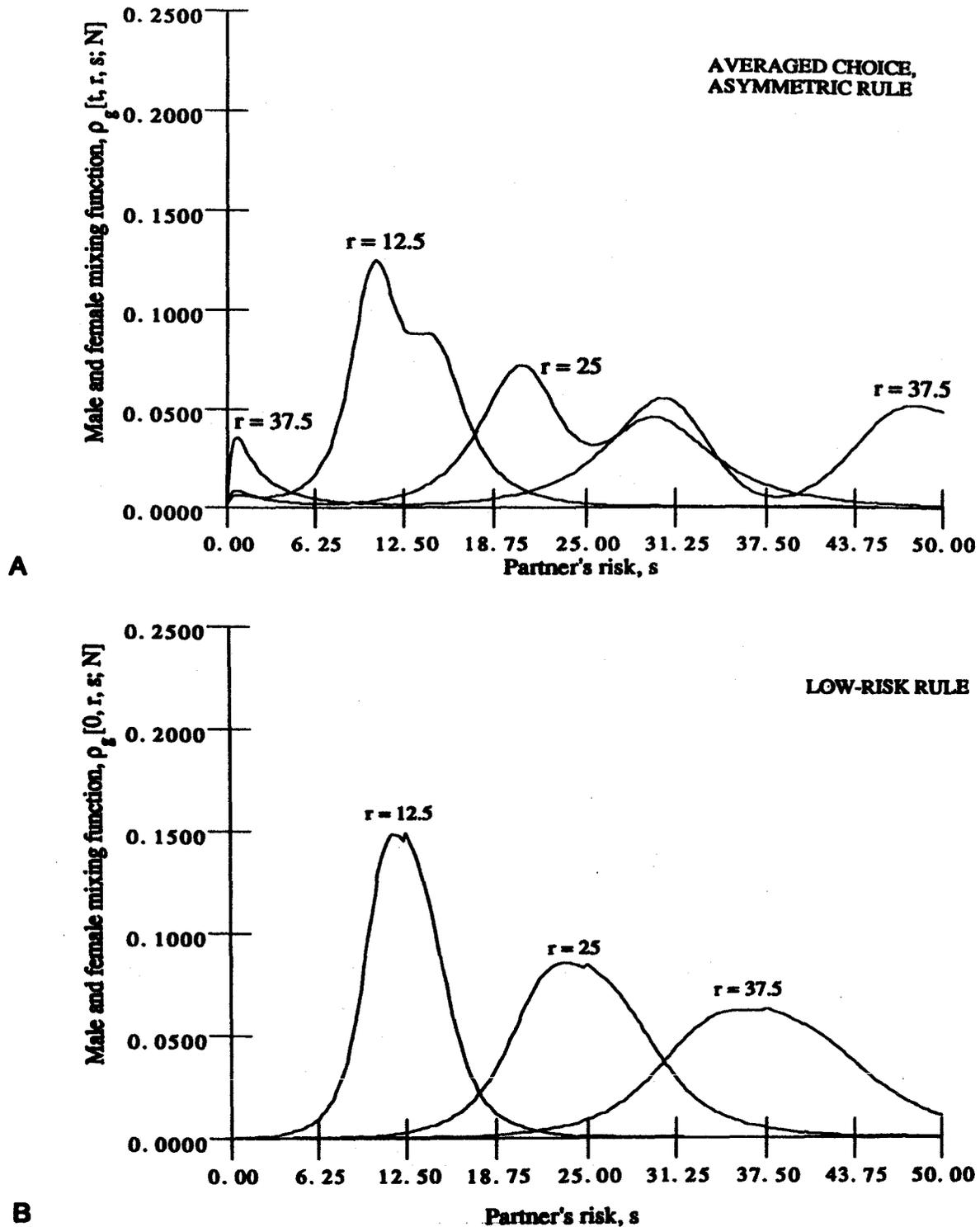


FIG. 3. The mixing functions obtained by using the same acceptance function and population distributions as in Fig. 2. **A:** the average of male and female choice in the asymmetric rule, as in Equation [13]. **B:** the low-risk rule of Equations [9] and [10]. In both cases the symmetry of the mixing rules and the populations implies that male and female mixing functions are the same.

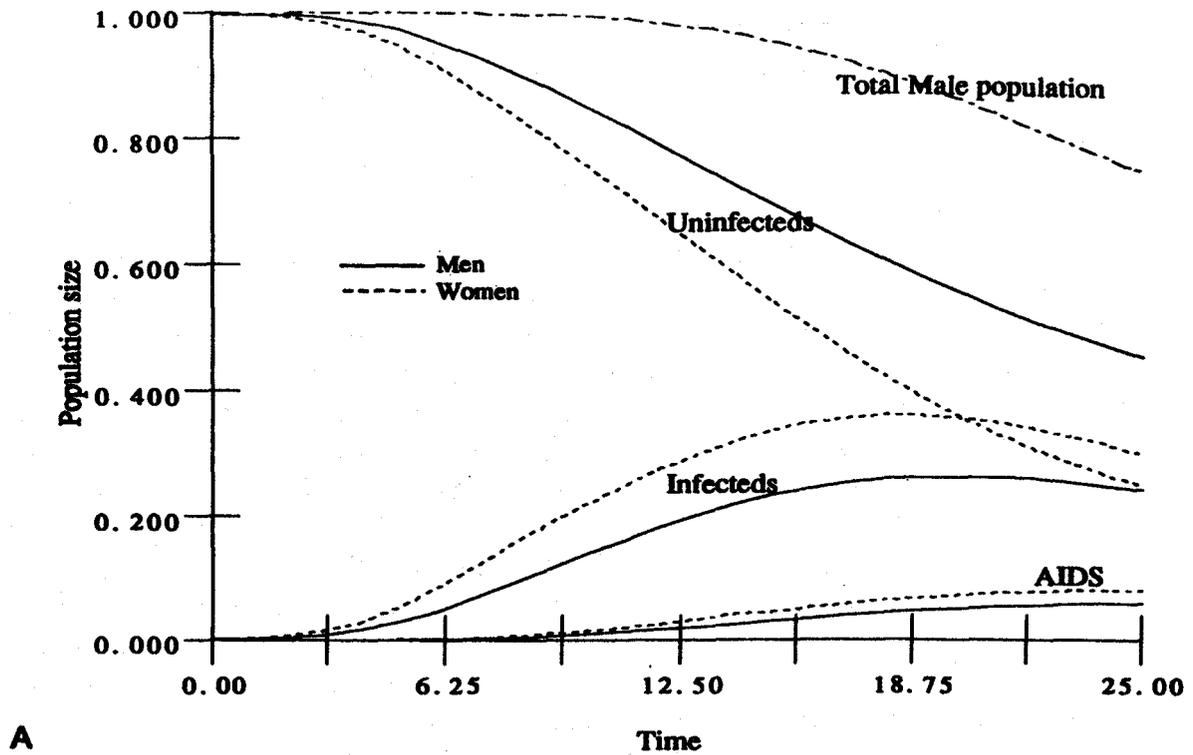
Baseline Calculations

For comparison purposes we set up a baseline simulation. We have tried to use reasonable parameter estimates but, given the relative uncertainty about many of the parameters and the simplicity of this model, the reader should exercise caution in interpreting the numbers. The baseline is intended only for comparison purposes. We take all male and female parameters to be identical, except the infectivities. We assume that men are four times as infectious as women, and take the infectivity multipliers in Equation [20] to be $\beta_M = 0.1$ and $\beta_F = 0.025$, so that the mean infectivity of men is 0.006 per contact. When multiplied by the factor $c_r(r,s)$ in Equation [21], to account for the larger number of contacts within low-risk partnerships compared with high-risk ones, the probability of transmission from an infected man to an uninfected female partner ranges from a high of 12%, when both are very low risk, to a low of 1.5% when both have risk 25, and transmission from women to men is one-fourth of this. We take initial male and female populations to be identical, with $n_r = 3$, and a mean risk of three partners per year, giving $a_F = a_M = 2$. We use the acceptance function of Equation [28], and the asymmetric rule with female choice, so that the initial mixing functions are as shown in Fig. 2.

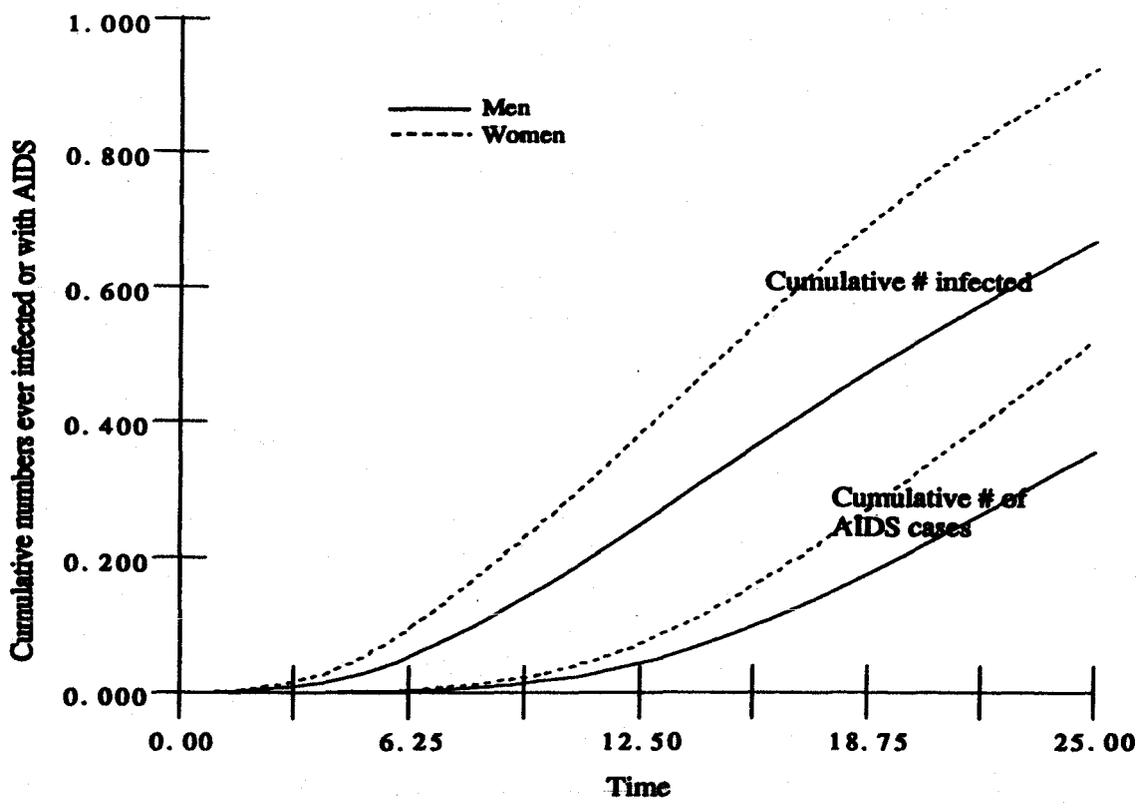
Figure 4A shows the change in the populations as a function of time for 25 years. Note that more women are infected than men (about 1.5 women per man in the early stages). Initial growth of infection is nonexponential, as in the homosexual model of ref. 8. The cumulative number of infecteds and AIDS cases initially grow as t^m , where m is between 2 and 3 (Fig. 4B). The infection eventually saturates, in the sense that the number of infected people begins to decline, but the susceptible population also continues to decline. AIDS cases remain a small fraction of the infected population at all times.

Figure 4C shows the infection as a function of risk, for the times 5, 10, 15, and 20. For men, the infection appears as a "wave" traveling from high to low risk, as it did in the homosexual model (9), although the wave is not as distinct. However, for women the wave is not distinct: the infection moves earlier and more intensely into the low-risk female populations than it does into the low-risk male populations. This clearly occurs because there are a lot more cross-risk contacts set up with this particular heterosexual mixing formulation, as seen in Fig. 2, than in the homosexual case (where assuming a narrow acceptance function created a situation in which most contacts were between individuals with similar risk values). Thus, in this heterosexual baseline, infected high-risk men are contacting and infecting low-risk women (and vice versa), and the epidemic does not stay isolated within the extremely high-risk groups. This mathematical cross-mixing may be an artifact of the asymmetric mixing rule, in which case the more rapid spread into low-risk groups might not be observed, or it may reflect the difficulty of the heterosexual partner-selection problem in the real world, in which case infections in low-risk women early in the epidemic should be relatively common.

Figure 4D shows the distribution over τ of the infecteds at different times. As time increases, the numbers infected increase both in magnitude and in duration of

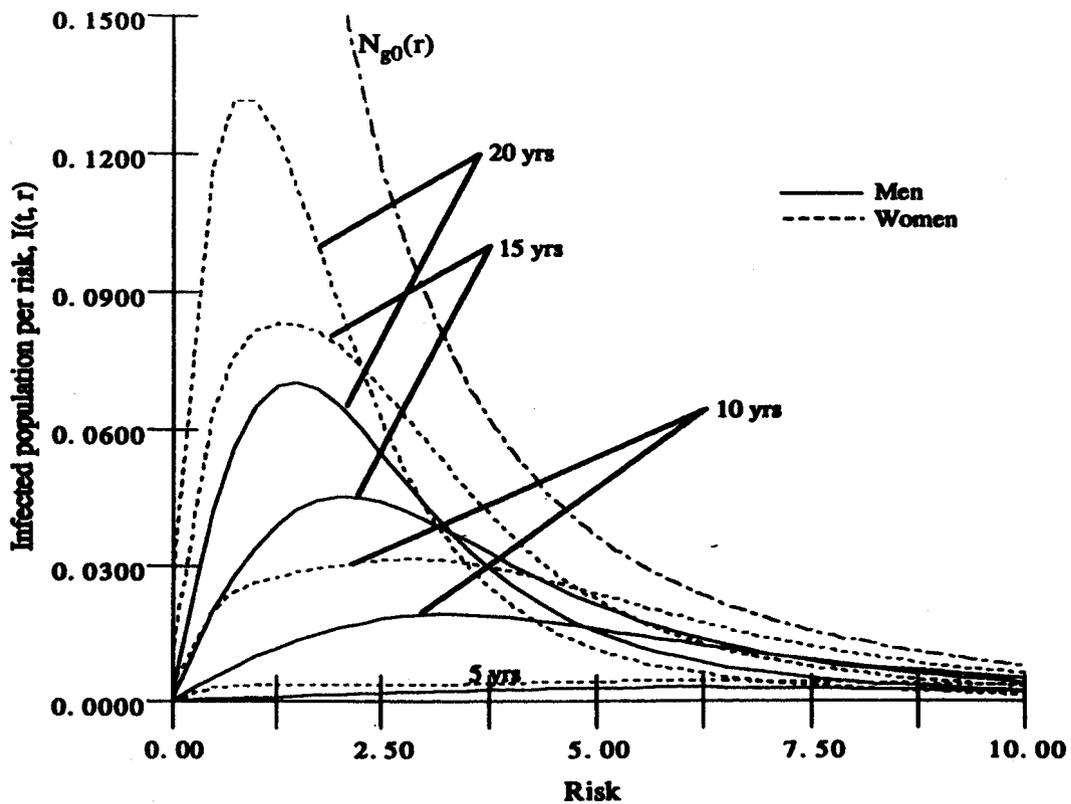


A

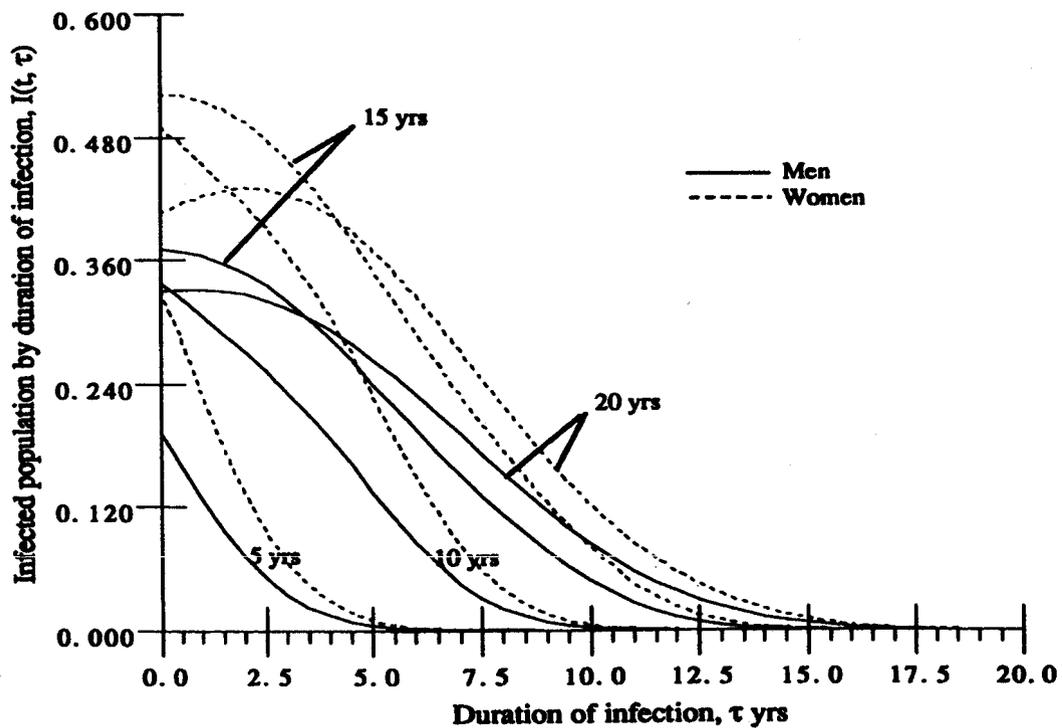


B

FIG. 4. The baseline simulation. Male populations are *solid lines* and female populations are *dashed*. **A:** The populations as a function of time. Populations are obtained by integrating over all risk and, for infecteds and AIDS cases, by integrating over the duration in the state. The *dashed-dot line* is the total male population. With these parameters, more than half of women become infected, and the epidemic in women saturates at about time $t=17$ years. **B:** The cumulative number infected and with AIDS, obtained by integrating the rate of infection and the



C



D

rate of developing AIDS over time (starting with the initial time up to the present) and over risk and duration. These numbers grow as t^m , with m around 3 or 4. C: The distributions of the infected populations over risk at intervals of 5 years. The distributions are obtained by integrating over all possible durations of infection. Note that the maximum point is at lower values of risk at each time slice, creating a "wave" of infection. D: The distribution of the infected population over duration of infection, obtained by integrating over risk.

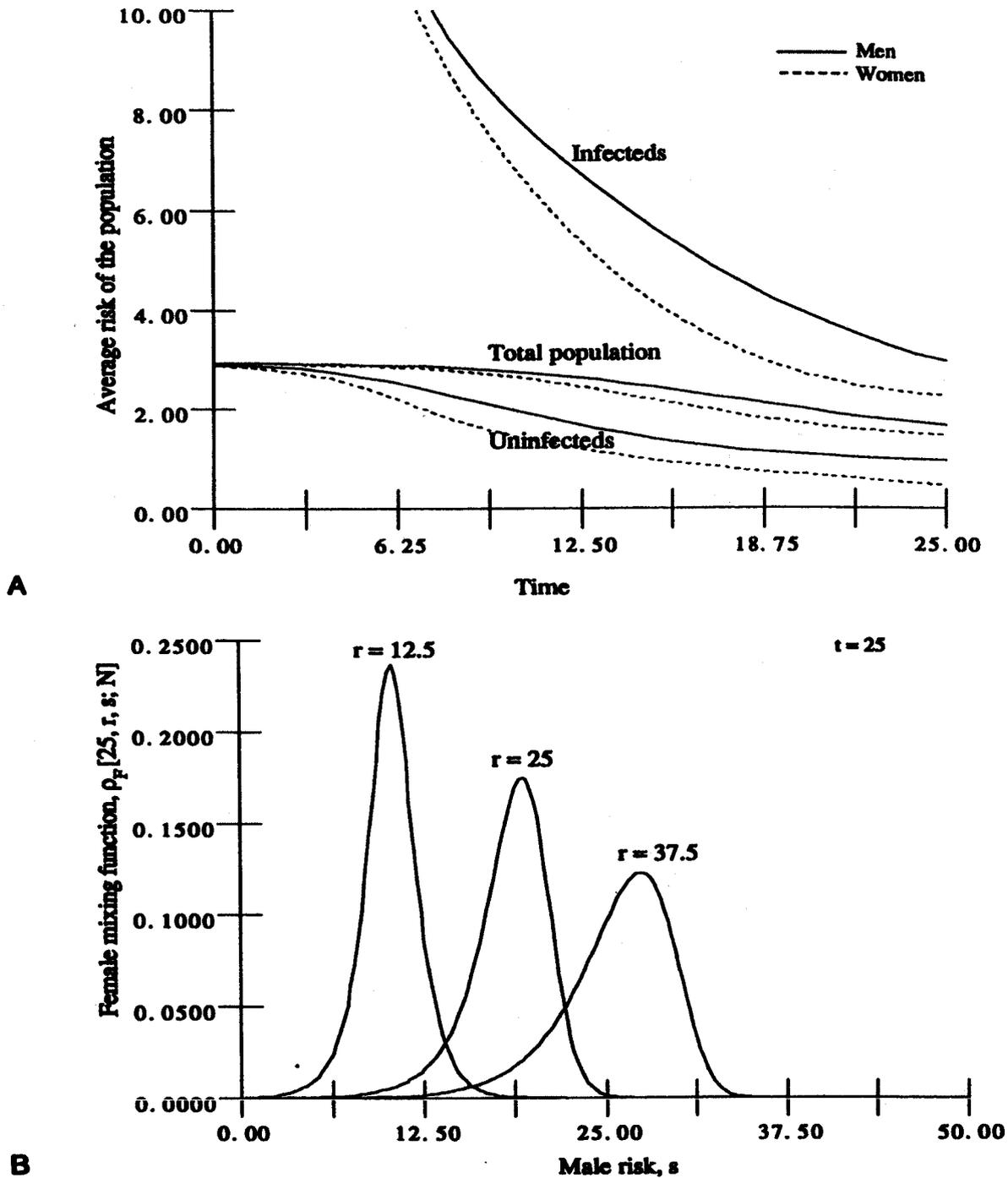


FIG. 5. Sexual behavior changes for the baseline scenario of Fig. 4. **A:** Changes in the mean risk with time. The mean risk of each population declines over time as the highest risk individuals are the most likely to die of AIDS. **B:** The distribution of the male partners of women at time $t=25$. **C:** The distribution of the female partners of men at $t=25$. The elimination of more high-risk women than men causes an even larger fraction of high-risk men to be paired with low-risk women than at the start of the simulation (see Fig. 2B).

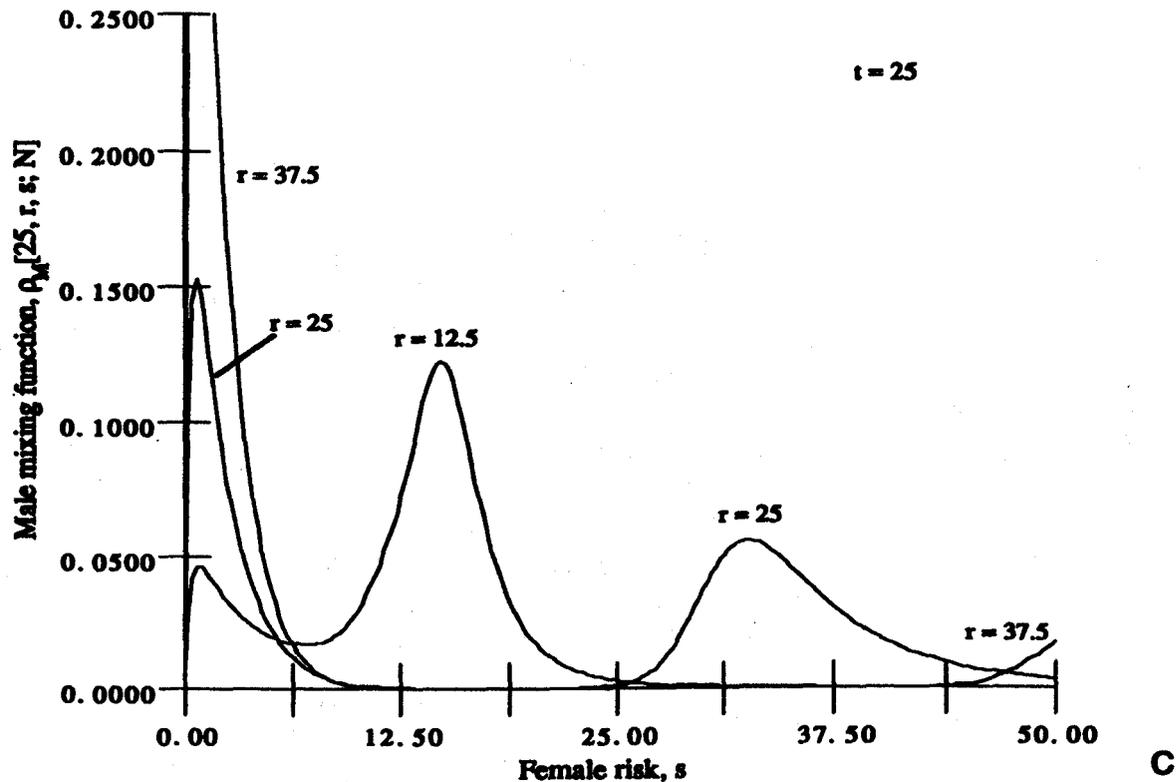


FIG. 5. Continued

infection. At large times, when saturation has begun, the number of newly infecteds begins to decline, whereas the number of long-term infecteds continues to increase.

As the population changes, the sexual behavior of the two populations also changes. The changes in mean risk are shown in Fig. 5A. We have scaled this plot so that changes in the mean risk for the full population are visible. Thus, the early behavior of the infected populations cannot be seen: what happens is that the initial mean risk for infected men and women immediately jumps to about 50 and 43, respectively, from the initial condition of 25 and then plummets as the infection wave moves into lower risk groups. Since most infected people have not yet developed AIDS by the end of 25 years of our calculated epidemic, the population means decline only slightly over this period. However, both the mean risk and the total population of women declines more than that of men, causing the adjustment factors given by Equation [6] to change significantly. The mixing at $t=25$ years is shown in Figs. 5B and 5C. Note that the greater loss of women, at lower risk levels than men, implies that more high-risk men pair with low-risk women than at the start of the calculation. The adjustments made by this rule with this mixing function seem somewhat unrealistic, because most of the partners of high-risk men are very low risk. We examine the effect of this choice of mixing rule under the heading Mixing Rule, below.

The Effect of i_F/i_M

The relative magnitude of the infectivity of males, $i_M(\tau)$, and of females $i_F(\tau)$, is a subject of much debate, although i_F is known to be the smaller of the two (as discussed earlier). Here we explore how this ratio affects our baseline scenario. We hold all parameters fixed, except the infectivity multipliers in Equation [20], β_M and β_F . In Fig. 6A we show the case where β_M is halved to 0.05 and β_F is left at the baseline value, and in Fig. 6B we show the case where β_M is left at baseline and β_F is halved. In both cases the epidemic is smaller than at baseline, and proceeds much more slowly, with the number of infections beginning to slow only at 25 years. However, these two cases have different effects on the epidemic. Halving the male infectivity decreases the number of women infected before time 16 by a factor of about $2\frac{1}{3}$, and roughly halves the number of men infected, so that the number infected is more similar in the two populations. Halving the female infectivity has the opposite effect, enhancing the difference between the two sexes.

What if the infectivities were even smaller? Decreasing β_M to the same value as β_F gives an epidemic that is nearly identical in terms of numbers infected in both male and female populations. The epidemic proceeds slowly, but nevertheless by year 25 about 10% of the population is infected. If, instead, β_M is left at baseline and β_F is taken to be one-quarter of baseline, the total fraction infected also is about 10%, but about three women are infected for every man (plots not shown).

Population Distributions

In the baseline scenario we took the initial male and female populations to be identical. Here we take the male population to be distributed as an inverse quartic for large risk, with $n_M = 4$. The mean risk is still assumed to be 3, giving $a_M = 4$. We thus have more low-risk and high-risk women than men, and more men lie in the middle region. This subtle difference sets up a different kind of mixing, shown in Figs. 7A and 7B, in which high-risk men are less prone to mix with low-risk women than when the distributions were the same, since there are more high-risk women to pair with. Having fewer men at high risk, but more at intermediate risk, creates a faster epidemic than the baseline case. The men at intermediate risk have more female partners at high risk than in the baseline case, acting as a bridge between high- and low-risk populations. This epidemic reaches saturation sooner in both sexes.

Random Mixing

In all previous sections we have assumed strong like-with-like preferences in partner selection. There are little data to support or contradict this assumption. If we suppose that the acceptance function is a constant, we obtain proportionate mixing, which is equivalent to the mixing from random partner selection, and results in the

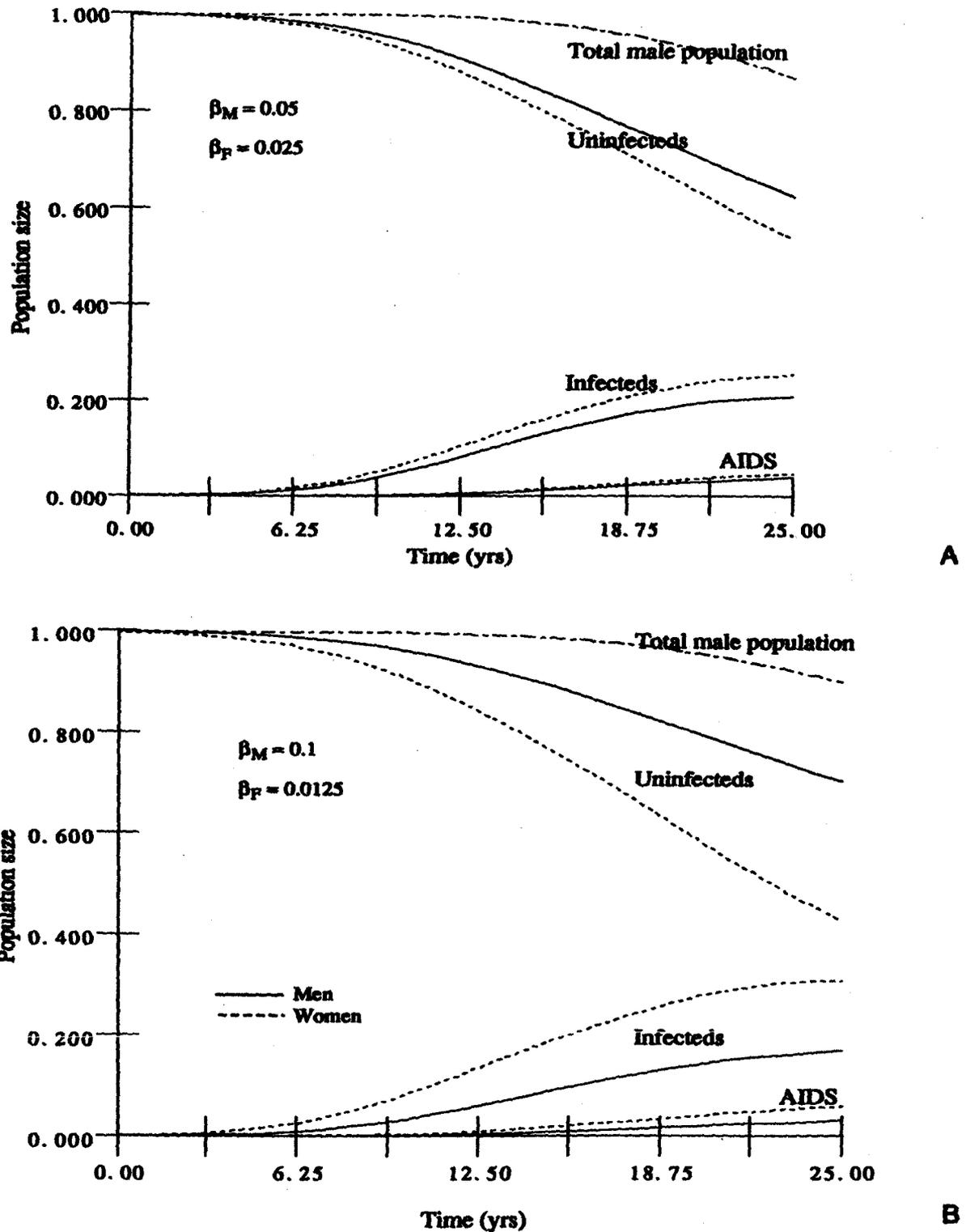


FIG. 6. The sensitivity of the baseline scenario to the infectivity multipliers, β_M and β_F of Equation [20]. **A:** $\beta_M = 0.05, \beta_F = 0.025$; **B:** $\beta_M = 0.1, \beta_F = 0.0125$. Both the total number of infecteds and the ratio of female to male infections are sensitive to the infectivities. Halving each infectivity more than halves the number of infecteds in the opposite sex, and roughly halves that of the sex affected.

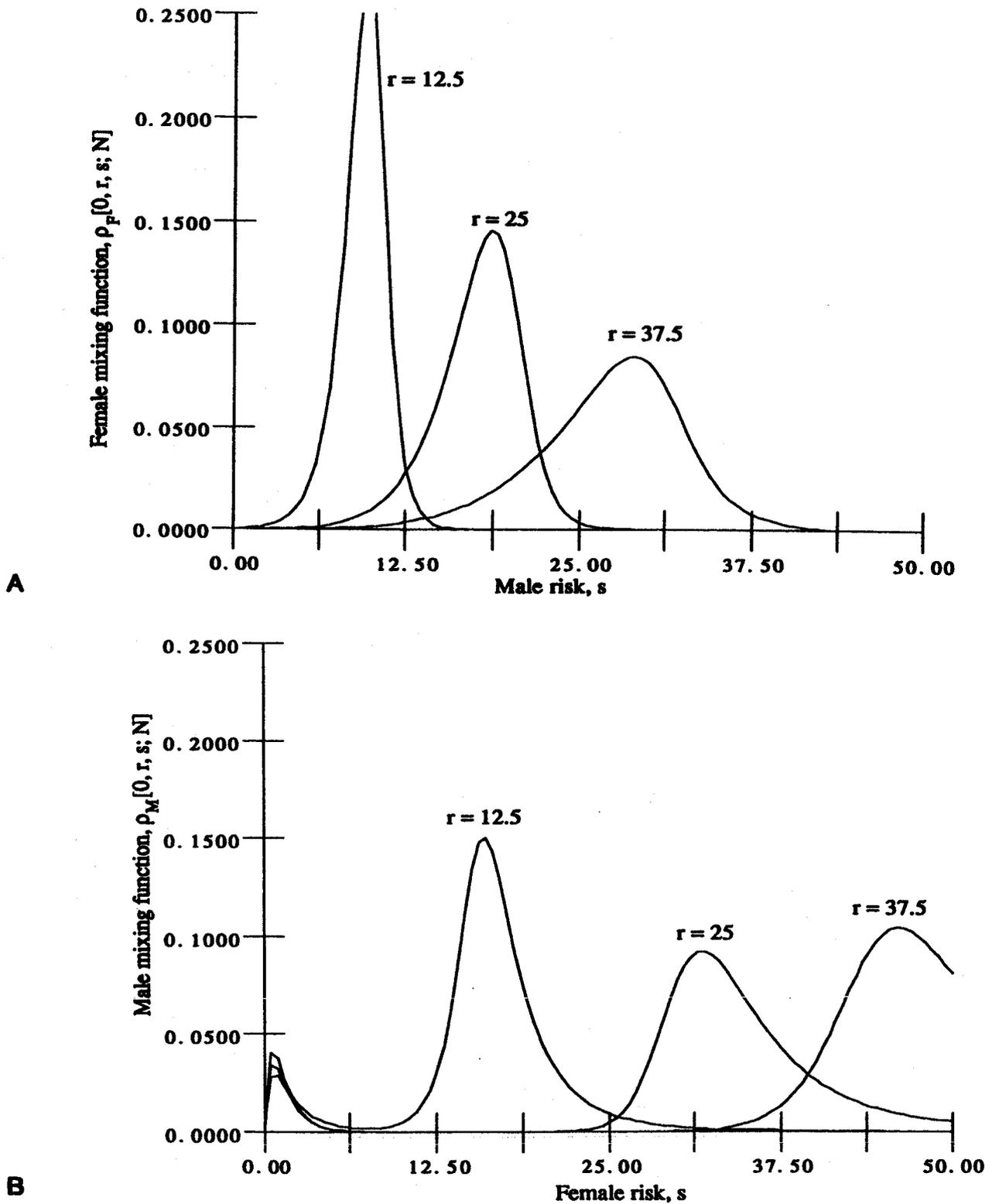


FIG. 7. The impact of the chosen initial and equilibrium population distribution function as specified by Equations [23] and [24]. Men are distributed with $n_M=4$ and $a_M=4$. Everything else is identical to the baseline. **A:** The initial distribution of the male partners of women; **B:** the initial distribution of the female partners of men; **C:** the populations as a function of time.

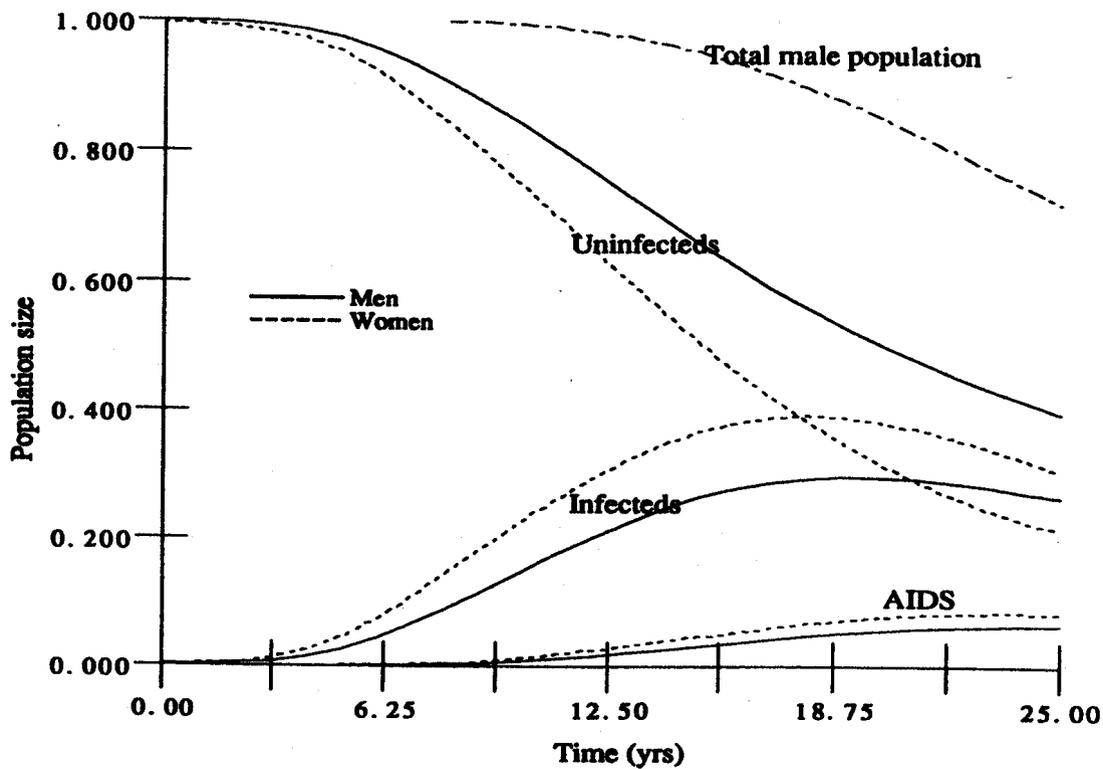


FIG. 7. Continued

scenario shown in Fig. 8. This result is similar to that previously seen in proportionate-mixing models of homosexual spread (8,9): the initial epidemic growth is exponential, and thus early on the epidemic is slower than in the baseline scenario, but quickly surpasses it. A much larger proportion of the population is affected, and the population is depleted more rapidly. Additionally, the epidemic does not proceed as a wave of infection from high to low risk, and a large fraction of moderate-risk people, especially women, are infected early in the epidemic.

Mixing Rule

If mixing is biased, it is not clear how that bias operates between the sexes. Because of the mathematical pairing constraints, we are forced to use a rule that is somewhat artificial to create biased mixing. What is the impact of the female-choice asymmetric mixing rule that we have been using? We ran the baseline scenario with the female-choice mixing replaced by the low-risk rule (Equations [9] and [10], the asymmetric rule (Equations [11] and [12]) with male choice, and the asymmetric rule with an average of male and female choice (as in Equation [13]). The initial mixing functions for these simulations are shown in Fig. 3. All the population sizes are similar to the baseline case early in the epidemic, until about the 10th year, after

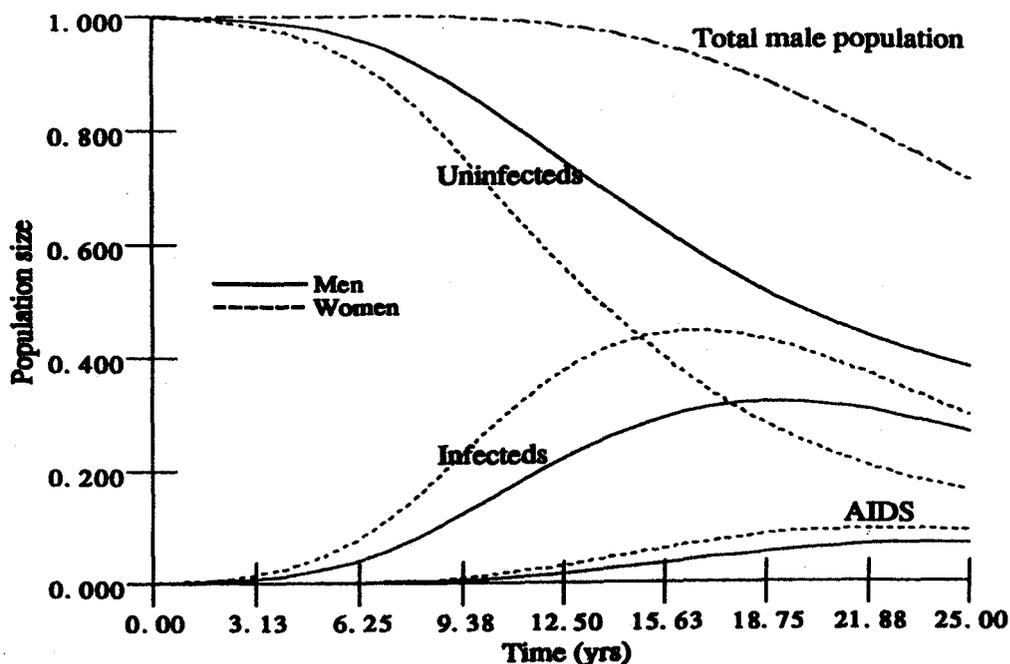


FIG. 8. Random mixing. Initially the number of infecteds and AIDS cases grows exponentially in time. Although initially the epidemic grows more slowly, over time the increased contacts between risk groups cause the total numbers infected to be greater than the baseline case.

which the low-risk rule and male-choice rule diverge with somewhat fewer people infected. Since the plots are similar, we do not show them.

The infection waves are much clearer in the low-risk mixing rule calculations, and the epidemic does not move as far into the low-risk population as in the baseline case. This is to be expected, since the low-risk rule provides more strongly biased mixing functions. It is less clear what is happening in the male-choice case to hold down infections.

The mixing function for each of these cases changes with time as the populations shift. Those of the low-risk rule change the most significantly, becoming highly discontinuous with time, but maintaining much more strongly biased mixing than any of the asymmetric rules.

Contacts per Partner

We have assumed that the probability of transmission from an infected to an uninfected partner decreases with the risk of both partners, since the average number of contacts would decrease. As explained earlier, it is not clear that the transmission probability does increase with increasing numbers of contacts. Consider the case where $c_p(r,s) = 10$, where the probability of transmission within a high-risk partnership is much higher than the baseline case, while being much lower within a low-risk partnership. The epidemic is modified substantially by this change: it is

initially much faster, but it is slower at long times. This slowdown occurs because fewer low-risk people become infected than in the baseline case (plot not shown).

SUMMARY

In this chapter we have begun to explore a heterosexual model of the spread of AIDS in which the population is distributed continuously according to partner-acquisition rates and duration of infection. Mixing between groups with different risk behavior was determined by partner availability and acceptability as specified by an acceptance function, plus an algorithm that matches male and female contacts. The growth rate of the modeled epidemic is determined largely by the social mixing patterns and the infectivity of infected men and women. When individuals select partners with behavior similar to their own, the epidemic proceeds as a "wave" from high-risk to low-risk populations. When men are more infectious than women, more women are infected than men.

The question of how to match contacts between risk groups when mixing is biased warrants a great deal of study. We have made assumptions, not based on data, about how this is done. This choice of assumptions clearly has a large impact on the model's behavior. In the absence of a vaccine or cure for AIDS, it is furthermore crucial to understand ways to change human behavior that are effective in slowing or stopping the epidemic.

We have not attempted to address questions about the heterosexual epidemic in the United States. To do this, we would need much more information about the infectivity of HIV and the sexual behavior of the population. There are, however, a multitude of other questions that remain unanswered about the transmission dynamics of this epidemic that can be addressed using models. These include the impact of social structures, including age, sex, sexual partner-acquisition rates, ethnicity, and religion, and the selection of sexual partners according to their characteristics. Migration and behavior changes, either in response to the epidemic or normal life fluctuations, also influence the epidemic spread. The interaction of these sociological factors with biological factors, such as the long and variable duration of infection, the variation of infectivity with disease progression, the impact of other sexually transmitted diseases, and the increasing use of treatments for AIDS, are yet more questions for continuing research.

APPENDIX: AVERAGE INFECTIVITY

In the text, we supposed that the infectiousness of an individual of gender g is given by $i_g(\tau/\tau_A)$, where τ is the time since infection and τ_A is the total time from infection to AIDS for this particular individual. We are assuming that the time to AIDS, τ_A , is independent of the time, t , and thus is not affected significantly by the development of new treatments. Here we show that this assumption implies that the average infectiousness of an individual infected at time τ is given by Equation [19].

The following calculations hold for each gender separately, so we will ignore the gender of the infectious individual, and leave off the subscripts. Let $\hat{I}(t, r, \tau, \tau_A)$ be the infected population at time t , distributed over time since infection, time to AIDS, and risk. Then the average infectivity of a person of risk r at time t who has been infected τ years is

$$i(t, r, \tau) = \int_0^{\infty} i_A(\tau/\tau_A) \frac{\hat{I}(t, r, \tau, \tau_A)}{I(t, r, \tau)} d\tau_A \quad [29]$$

where the ratio of $\hat{I}(t, r, \tau, \tau_A)$ to $I(t, r, \tau)$ is the probability that a person of risk r infected for τ years will develop AIDS at τ_A years after infection. To show that Equation [19] holds for each gender, we need to show that $\hat{I}(t, r, \tau, \tau_A)/I(t, r, \tau)$ is zero for $\tau_A < \tau$ and that for $\tau_A > \tau$:

$$\frac{\hat{I}(t, r, \tau, \tau_A)}{I(t, r, \tau)} = \frac{C'(\tau_A)}{1 - C(\tau)} \quad [30]$$

for all r and t , where $C(\tau)$ is the probability that a newly infected person will develop AIDS within the first τ years after infection. Since everyone with $\tau_A < \tau$ will already have developed AIDS and left the infected population, the first requirement is obvious, that is,

$$\hat{I}(t, r, \tau, \tau_A) = 0, \text{ for } \tau_A < \tau. \quad [31]$$

There are two ways to see that Equation [30] holds. First, note that the ratio of $\hat{I}(t, r, \tau, \tau_A)$ to $I(t, r, \tau)$ is the conditional probability that someone infected for τ units of time will develop AIDS after being infected τ_A units of time, given that they have not developed AIDS before τ . When $\tau_A > \tau$, this is the probability of developing AIDS at time τ_A , divided by the probability of not developing AIDS before time τ .

The other way to see this is to note that if the duration of infection of a newly infected person is independent of that of the person who just infected her/him, newly infecteds are distributed by

$$\hat{I}(t, r, 0, \tau_A) = \lambda[t, r; U, \Pi]U(t, r)C'(\tau_A). \quad [32]$$

We also assume that the initial infected population is distributed evenly in τ_A :

$$\hat{I}(0, r, \tau, \tau_A) = \frac{C'(\tau_A)}{1 - C(\tau)} I(0, r, \tau). \quad [33]$$

Then $I(t, r, \tau)$ satisfies Equation [1] and, for $\tau < \tau_A$, $\hat{I}(t, r, \tau, \tau_A)$ satisfies

$$\frac{\partial \hat{I}(t, r, \tau, \tau_A)}{\partial t} + \frac{\partial \hat{I}(t, r, \tau, \tau_A)}{\partial \tau} = -\mu \hat{I}(t, r, \tau, \tau_A) \quad [34]$$

Solving this and the equation for the infecteds in system [1], we find that for $t > \tau$

$$\begin{aligned} I(t, r, \tau) &= \lambda[t - \tau, r; U, \Pi]U(t - \tau, r)\exp(-\mu\tau - \int_0^{\tau} \gamma(x)dx) \\ &= \lambda[t - \tau, r; U, \Pi]U(t - \tau, r)e^{-\mu\tau} (1 - C(\tau)), \end{aligned} \quad [35]$$

and

$$\dot{I}(t, r, \tau, \tau_A) = \lambda[t - \tau, r; U, \Pi]U(t - \tau, r)C'(\tau_A)e^{-\mu\tau}, \quad [36]$$

whereas for $t < \tau$:

$$\begin{aligned} I(t, r, \tau) &= I(0, \tau - t, r) \exp\left(-\mu t - \int_{\tau-t}^{\tau} \gamma(x) dx\right) \\ &= I(0, \tau - t, r) e^{-\mu t} \frac{1 - C(\tau)}{1 - C(\tau - t)}, \end{aligned} \quad [37]$$

and

$$\dot{I}(t, r, \tau, \tau_A) = I_0(\tau - t, r) \frac{C'(\tau_A)}{1 - C(\tau - t)} e^{-\mu t}. \quad [38]$$

Thus we have the desired relationship.

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REFERENCES

1. Quinn TC. AIDS in Africa. *AIDS Updates* 1991;4:3-10.
2. Green TA, Karon JM, Nwanyanwu OC. Changes in AIDS incidence trends in the United States. *J AIDS* 1992;5:547-55.
3. Sattenspiel L. Population structure and the spread of disease. *Hum Biol* 1987;59:411-38.
4. Nold A. Heterogeneity in disease modeling. *Math Biosci* 1980;52:227-40.
5. Hethcote HW, Yorke JA, Nold A. Gonorrhea modeling: a comparison of control methods. *Math Biosci* 1982;58:93-109.
6. Hethcote HW, Yorke JA. *Gonorrhea: transmission dynamics and control*. Lecture Notes in Biomathematics, Vol. 56. New York: Springer-Verlag; 1984:1-105.
7. Anderson RM, May RM, Medley GF, Johnson A. A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *IMA J Math Appl Med Biol* 1986;3:229-63.
8. Hyman JM, Stanley EA. Using mathematical models to understand the AIDS epidemic. *Math Biosci* 1988;90:415-74.
9. Hyman JM, Stanley EA. The effect of social mixing patterns on the spread of HIV. In: Castillo-Chavez C, ed. *Mathematical approaches to ecological and environmental problem solving*. Lecture Notes in Biomathematics, Vol. 81. New York: Springer-Verlag; 1989:190-219.
10. Jacquez J, Simon C, Koopman J, Sattenspiel L, Perry T. Modeling and analyzing HIV transmission: the effect of contact patterns. *Math Biosci* 1988;92:119-99.
11. Longini IM, Clark WS, Haber M, Horsburg R. The stages of HIV infection: waiting times and infection transmission probabilities. In: Castillo-Chavez C, ed. *Mathematical and statistical approaches to AIDS epidemiology*. Lecture Notes in Biomathematics, Vol. 3. New York: Springer-Verlag; 1989:111-37.

12. Colgate SA, Stanley EA, Hyman JM, Layne SP, Qualls Q. A behavior based model of the initial growth of AIDS in the United States. *Proc Natl Acad Sci* 1989;86:4793-7.
13. Stanley EA, Hyman JM, Colgate Sa, Layne SP. A risk based heterosexual model of the spread of HIV. Vth International Conference on AIDS, Montreal, Canada, 1989 (abst Thy.A.P.66).
14. Hyman JM, Stanley EA. A heterosexual model for the AIDS epidemic with biased social mixing. *Los Alamos National Laboratory Technical Report* 1989;LA-UR-90-58.
15. Stanley EA. Interagency working group model equations for the transmission dynamics of HIV/AIDS. *Los Alamos National Laboratory Technical Report* 1990;LA-UR-90-2807.
16. Castillo-Chavez C, Busenberg S. On the solution of the two-sex mixing problem. In: Busenberg S, Martelli M, eds. *Proceedings of the international conference on differential equations and applications to biology and population dynamics*. Lecture Notes in Biomathematics, Vol. 92. New York: Springer-Verlag; 1991:80-98.
17. Stanley EA. Partner selection in heterosexual population. *Proceedings of the Third International Conference on Mathematical Population Dynamics* Paris, June 1992.
18. Kirschner D. Mathematical modeling of the AIDS virus in epidemiology and immunology. Dept. of Mathematics, Tulane University; 1991.
19. Hadler KP. Pair formation in age-structured populations. *Acta Appl Math* 1989;14:91-102.
20. Le Pont F, Blower SB. HIV, heterosexual transmission, and the supply and demand dynamics of sexual behavior. *J AIDS* 1991;4:987-99.
21. Koopman JS, Simon C, Jacquez J, Sattenspiel L, Park T. Sexual partner selectiveness effects on homosexual HIV transmission dynamics. *J AIDS* 1988;1:486-504.
22. Morlat P, Parniex P, Druard D, et al. Women and HIV infection: a cohort study of 483 HIV-infected women in Bordeaux, France, 1985-1991. *AIDS* 1992;6:1187-94.
23. Medley GF, Anderson RM, Cox DR, et al. Incubation period of AIDS in patients infected via blood transfusion. *Nature* 1987;238:719-21.
24. Wiley JA, Herschkorn SJ, Padian NS. Heterogeneity in the probability of HIV transmission per sexual contact: the case of male-to-female transmission in penile-vaginal intercourse. *Stat Med* 1989;8:93-102.
25. Pederson C, Nielson CM, Vestergaard BF, Gerstoft J, Krogsgaard K, Nielsen JO. Temporal relation of antigenaemia and loss of antibodies to core antigens to development of clinical disease in HIV infection. *Br Med J* 1987;295:567-9.
26. Gruters RA, Terpstra FG, De Goede REY, et al. Immunological and virological markers in individuals progressing from seroconversion to AIDS. *AIDS* 1991;5:837-44.
27. Lazzarin A, Saracco A, Musicco M, Nicolosi A. Man-to-woman sexual transmission of HIV. *Arch Intern Med* 1991;151:2411-6.
28. De Vincenzi I. Letter to *JAMA*. 1992;267:1919.
29. Maternal factors involved in mother-to-child transmission of HIV-1: report of a consensus workshop. Siena, Italy, Jan. 17-18, 1992. *AIDS* 1992;5:1019-29.
30. Henin Y, Mandelbrot L, Henrion R, Pradinaud R, Coulaud JP, Montagnier L. Virus excretion in the cervicovaginal secretions of pregnant and nonpregnant HIV-infected women. *J AIDS* 1993;6:72-75.
31. Johnson AM, Laga M. Heterosexual transmission of HIV. *AIDS* 1988;2(Suppl 1):S49-S56.
32. Padian NS, Shiboski S, Jewell NP. Female-to-male transmission of HIV. *JAMA* 1991;266:1664-7.
33. Simonsen JN, Cameron DW, Gakinya MN, et al. HIV infection among men with STDs. *N Engl J Med* 1988;319:274-8.
34. Peterman TA, Stonebrunner RL, Allen JR, Jaffe HW, Curran JW. Rise of human immunodeficiency virus transmission for heterosexual adults with transfusion-associated infections. *JAMA* 1988;259:55-8.
35. Sewenkambo JN, Carlswell JW, Mugerwa, et al. HIV infection through normal sexual contact in Uganda. *AIDS* 1987;1:113-6.
36. Ragni MV, Kingsley LA, Nimorwicz P, et al. HIV heterosexual transmission in hemophilia couples: lack of relation to T4 number, clinical diagnoses, or duration of HIV exposure. *J AIDS* 1989;2:557-63.
37. Palenicek J, Fox R, Margolick J, et al. Longitudinal study of homosexual couples discordant for HIV-1 antibodies in the Baltimore MACS study. *J AIDS* 1992;5:1204-23.
38. Chiodo F, Marinacci G, Costiliola. Risk factors in heterosexual transmission of HIV. 6th International Conference on AIDS in San Francisco. 1990 (abst Th.C.583).
39. Bertrand JT, Makani B, Hassig SE, et al. AIDS-related knowledge, sexual behavior, and condom use among men and women in Kinshasha, Zaire. *Am J Public Health* 1991;81:3-58.

40. Johnson AM, Wadsworth J, Elliot P, et al. A pilot study of sexual lifestyle in a random sample of the population of Great Britain. *AIDS* 1989;3:135-41.
41. State of California Department of Health Services Office of AIDS. *Planning for the AIDS epidemic in California: a population-based assessment of knowledge, attitudes and behaviors*. Prepared by Communications Technologies; 1988.
42. Træen B, Lewin B. Casual sex among Norwegian adolescents. *Arch Sex Behav* 1992;21:253-69.
43. Fullilove MT, Wiley J, Fullilove RE, et al. Risk for AIDS in multiethnic neighborhoods in San Francisco, California: the population-based AMEN study. *West J Med* 1992;157:32-40.
44. Kahaner D, Moler C, Nash S. *Numerical methods and software*. Englewood Cliffs, NJ: Prentice Hall; 1989.