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TITLE **MATHEMATICAL MODELS OF THE AIDS EPIDEMIC: AN HISTORICAL PERSPECTIVE**

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Mathematical Models of the AIDS Epidemic: an Historical Perspective

INTRODUCTION

Researchers developing mathematical models of the spreading of HIV, the Human Immunodeficiency Virus that causes AIDS, hope to achieve a number of goals. These goals may be classified rather broadly into three categories: understanding, prediction, and control. Understanding which are the key biological and sociological processes spreading this epidemic and leading to the deaths of those infected will allow AIDS researchers to collect better data and to identify ways of slowing the epidemic. Predicting the groups at risk and future numbers of ill people will allow an appropriate allocation of health-care resources. Analysis and comparison of proposed control methods will point out unexpected consequences and allow a better design of these programs. The processes which lead to the spread of HIV are biologically and sociologically complex. Mathematical models allow us to organize our knowledge into a coherent picture and examine the logical consequences, therefore they have the potential to be extremely useful in the search to control this disease.

AN HISTORICAL CAUTION

However, we need to be cautious about what it is possible to achieve with epidemic models. If we examine the history of modeling of infectious diseases, we can learn quite a lot about what can and cannot be done with models[4,13]. Models have been developed to study the mechanisms behind disease spread and predict the spread of a large number of infectious diseases. Many insights have been gained by studying epidemics using models, some of which have been useful and some of which have been misleading. However, models have been largely unsuccessful at predicting future disease spread. Only models which have been built on a solid knowledge of the specific disease of interest have proved useful in the actual prevention and control of disease. For the most part, even the successful models have primarily provided some key epidemiological concepts, which tend to seem obvious once they've been pointed out.

One of the basic concepts behind epidemic models, the mass action law, was formulated by Hamer in 1906[12]. This principle, that the rate that people are infected is proportional to the number of susceptible individuals times the number infected times the contact rate, is a key insight into the transmission of infectious agents and explains the shape of most epidemic curves: initial exponential growth, followed by a slowdown as the population saturates, and a die-off as the infecteds all recover or die.

Sir Ronald Ross wrote down the first equations based on transmission dynamics in 1911[24]. His simple malaria model showed that malaria can be controlled without killing off every mosquito, a point that was hotly debated at the time. Although Ross' conclusion was not accepted until malaria was actually controlled in the field, his concept of a threshold below which a disease dies out became one of the fundamental concepts in epidemiology. Ross further developed his model to show that malaria can be controlled in a region despite mosquito diffusion from neighboring, uncontrolled, regions. MacDonald[20] found that control of adult mosquitoes is more effective than larval control, using transmission models that took account of the effects of immunity. Since then, models of malaria have been used to examine more detailed questions of annual cycles, insecticide use, age-dependent immunity, etc., but none have had the impact of these early studies[8].

Models have probably been used the most in the control and prevention of malaria. However, there are a number of other examples where they have had some impact on public health policies. Hairston showed the importance of rats as reservoirs for schistosomiasis and gave a coherence to the epidemiological data[11]. Hethcote, Yorke and Nold[13] showed that a core group of highly promiscuous heterosexuals could maintain gonorrhea, and that contact tracing is a more efficient means of controlling its spread than routine screening: this has changed the focus of control programs in the U.S. and allowed this disease to be controlled in many groups. Anderson and May's age-structured models of measles[1] were used to guide the design of vaccination programs in Great Britain.

Models which have been useful for public health policy have primarily been simple models that provided useful qualitative insights. One reason for this is that

epidemiologists rarely care to deal with complicated mathematics, and mathematicians rarely understand enough about epidemiology to build useful models. Another reason is that the more detailed and sociologically correct a model becomes, the less robust to changes in parameter values it will tend to be. This bias toward oversimplified models can be a problem when some of the more important effects are neglected. For example, even though models indicated that it would be possible to eliminate smallpox by vaccinating a large fraction of the population, this herd immunity approach had to be abandoned in favor of the more ad hoc procedure of case finding and of vaccination of visitors to a region. It is believed that heterogeneities in population densities and contact patterns, neglected in the model, caused predictions to be invalid. Hethcote and Van Ark[14] argue that the core/noncore concept of the gonorrhea model need to be applied, with the two groups being cities and villages with nonproportionate mixing between them. The same neglect of spatial heterogeneity proved a disaster for the above-mentioned malaria models of MacDonald: despite the useful qualitative insight, his predictions that malaria could be eliminated proved incorrect.

One intriguing characteristic of epidemic models has been their ability to almost explain the nearly periodic (slightly chaotic) nature of many diseases. Invariably, the model exhibits damped periodic (or chaotic) behavior. The periodic nature of diseases is thus an almost obvious aspect of the disease transmission and recovery process. Finding the key to undamped, continuous oscillations has been nontrivial. Recently, Schenzle[22] showed that the variation of contact rates with the school year will give stable oscillations for measles in an age-structured population, with period 1 year for England and 2 years for Germany. Thus a slightly more complex, but very realistic, model was able to provide a likely explanation for a phenomenon that simple models could not explain.

One exception to the rule that models are primarily useful for qualitative insights into the spreading of a disease is the influenza models of Baroyan, et al.[3]. These models, which include extensive work on contact rates between cities, agree remarkably well with epidemics in Russia, and have been successfully applied to the spread of the Hong Kong flu in 1968-69. A review of this work, and presentation of the model, are given in Longini[19]. This is a very hopeful instance where good modelers working in conjunction with epidemiologists have been able to do both qualitative and quantitative predictions.

This abbreviated history shows that models can be useful if they go hand-in-hand with a strong understanding of the disease. They will primarily allow us to check that our assumptions about a disease process lead to logical and reasonable conclusions, and thus provide us with useful insights into the mechanisms behind disease spread. This will be best achieved if there is a good interaction between modelers and epidemiologists.

AIDS, SOME BASIC CONCEPTS[23]

HIV is spread by sexual contact, blood and blood products, and from mother to child during pregnancy or breast-feeding. Because the virus is spread by blood, IV drug users spread it by sharing needles and other equipment, and it is also spread by accidents leading to blood injection. A number of studies of household contacts of HIV infected people, and of people living in regions with high mosquito populations have been unable to document a single case where the virus could only have have been spread by insects or by normal, nonsexual contact. However, there have been a few cases where the virus has been spread by skin or eye contact with blood.

Except for cases when large amounts of blood or blood products are transferred, the average probability of becoming infected from a single contact with an infected person is small, on the order of 10^{-3}-10^{-4} for a sexual contact or needle-stick injury. A mother will transfer infection 20-50% of the time to her fetus. There is growing evidence that the infectivity of people is extremely variable, however. Not only can the presence of genital ulcers increase infectivity (and susceptibility?), but infectivity and/or susceptibility may vary with disease stage or strain of the virus, between circumcised and uncircumcised men, with the use of birth control pills, and between individuals for many unknown reasons.

Once infected, the immune system and/or the nervous system of the infected person is slowly destroyed, leading eventually to AIDS and death. The time from infection to major symptoms is different for each individual. Adults take at least 2 years to develop AIDS, and about 50% develop AIDS by 10 years after infection, with most of the rest having serious immune deterioration at th t point. It is not known if some small fraction (at most 10of people are resistant to the virus and will never develop serious problems. Once AIDS develops, the average time to death is about 13 months, with AZT prolonging life for 6 months to a year in those who can tolerate it.

It is not known why the time from infection to AIDS, and the infectivity of people, are so variable. Despite all that has been learned about this virus, the processes that lead to immune and brain deterioration are still poorly understood.

TWO SIMPLE MODELS FOR THE SPREAD OF HIV

Let us now consider the transmission of HIV by sex and needle-sharing. I will start by presenting two very simplified models of this spread, and then proceed to discuss how they can be expanded to include some of the special features of AIDS.

One way of modeling the epidemic is shown as the model 1 flow chart in Figure 1. We can divide the at-risk population into uninfected susceptibles, $S(t)$, pre-AIDS infected people, $I(t)$, and AIDS cases, $A(t)$. Assuming that AIDS cases stop spreading HIV, susceptibles become infected through contacts with infecteds

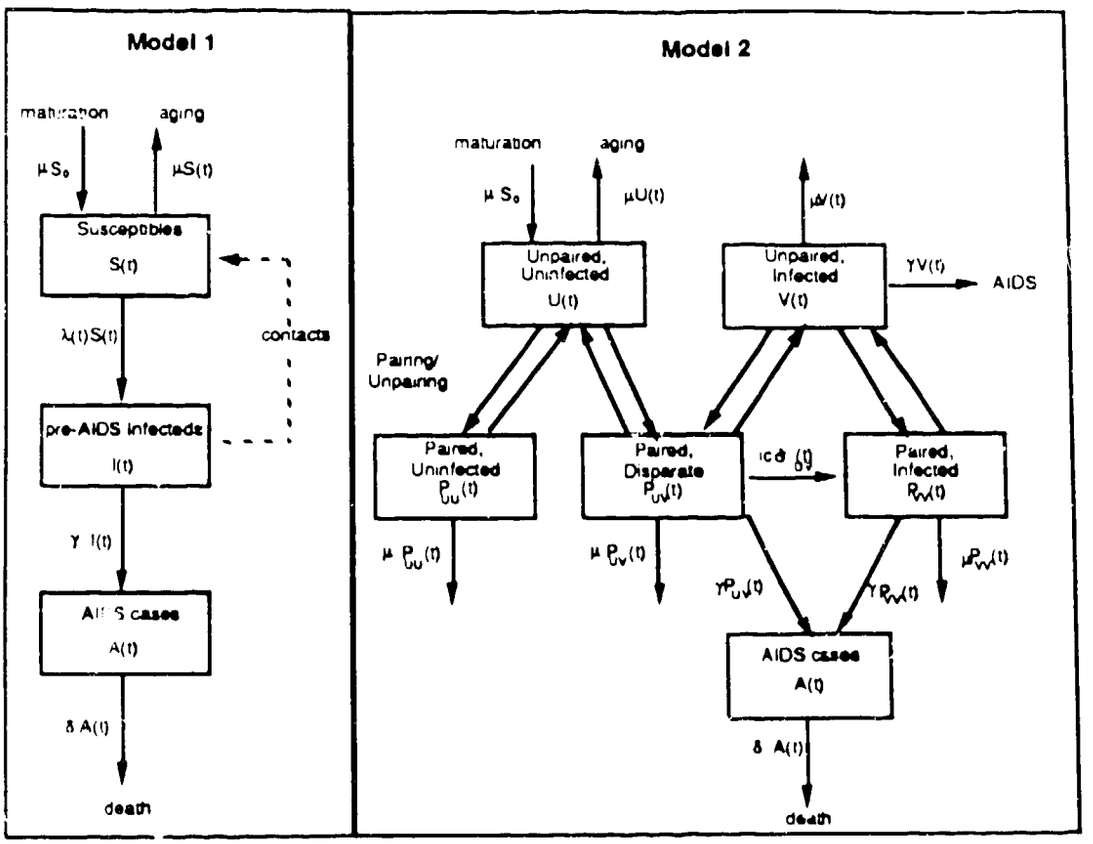

FIGURE 1 The flow of people in the simple models (1) and (2)

at some rate $\lambda(t)$ per susceptible. Infected people develop AIDS at a rate γ per infected, and AIDS cases die at a rate δ per person. There is also some rate background rate of ageing or dying, μ per person, that takes people out of the susceptible and infected populations, and some maturation rate, μS_0, that brings susceptibles into the population (if there were no HIV present, then the population would equilibrate at S_0 susceptibles). Under these conditions, we obtain the equations

$$\frac{dS}{dt} = \mu(S_0 - S(t)) - \lambda(t)S(t) , \tag{1a}$$

$$\frac{dI}{dt} = \lambda(t)S(t) - (\mu + \gamma)I(t) , \tag{1b}$$

$$\frac{dA}{dt} = \gamma I(t) - \delta A(t) \ . \tag{1c}$$

Infections are transferred by either sexual or needle-sharing contacts between what we shall term partners. When a new partner is chosen, there is some probability, $I(t)/(S(t) + I(t))$, that that partner is infected. There will then be c contacts between the two people, and probability i of transferring the infection with each contact. If we are dealing with a population which has a high partner-turnover rate and few contacts per partner, then the fact that the probability of transferring HIV per contact is small ($i \ll 1$) implies that we can use

$$\lambda(t) = icp\frac{I(t)}{I(t) + S(t)} \ , \tag{1d}$$

where p is the average number of new partners per unit time for an individual in our

population. The above model, which has been used by many groups as a basis for model building, focuses on the risk to an uninfected individual. Another perspective has been taken by Klaus Dietz[9], who suggests that we should focus on the transmission within partnerships. Model 2 in Figure 1 shows the flow chart for this model. Dietz divides the population into six basic classes. Before AIDS there are 2 classes, those in partnerships and those not in partnerships. With the introduction of HIV, there can now be infected, $V(t)$, and uninfected, $U(t)$, people who are not paired, uninfected pairs, $P_{UU}(t)$, disparate pairs, $P_{UV}(t)$, and infected pairs, $P_{VV}(t)$. There can also be AIDS cases, $A(t)$, and we shall assume that pairs dissolve when one person gets AIDS. People form pairs at a rate ρ per person, and dissolve them at a rate σ per pair. Infection is transferred within the disparate pairs, at a rate $c\sigma i$, where $c\sigma$ is the frequency of contacts within the pair. This then gives the system

$$\frac{dU}{dt} = \mu S_o - (\mu + \rho)U(t) + 2(\sigma + \mu)P_{UU}(t) + (\mu + \sigma + \gamma)P_{UV}(t) \ , \tag{2a}$$

$$\frac{dV}{dt} = -(\mu + \rho + \gamma)V(t) + 2(\sigma + \mu + \gamma)P_{VV}(t) + (\mu + \sigma)P_{UV}(t) \ , \tag{2b}$$

$$\frac{dP_{UU}}{dt} = 2\rho\frac{U^2(t)}{U(t) + V(t)} - (\sigma + 2\mu)P_{UU}(t) \ , \tag{2c}$$

$$\frac{dP_{UV}}{dt} = 4\rho\frac{U(t)V(t)}{U(t) + V(t)} - (\sigma + 2\mu + \gamma + ic\sigma)P_{UV}(t) \ , \tag{2d}$$

$$\frac{dP_{VV}}{dt} = 2\rho\frac{V^2(t)}{U(t) + V(t)} - (\sigma + 2\mu + 2\gamma)P_{VV}(t) + ic\sigma P_{UV}(t) \ , \tag{2e}$$

$$\frac{dA}{dt} = \gamma(V(t) + P_{UV}(t) + 2P_{VV}(t)) - \delta A(t) \ . \tag{2f}$$

This formulation takes better account of the transmission within long-term relationships than does system (1). It becomes, however, more complex than is really necessary when we start dividing people up into groups, as we shall do in the next section.

A MORE COMPLEX MODEL

There are a number of features of AIDS that neither of the above systems accounts for. There is, for one thing, a highly variable duration of infection. The constant rate of conversion from infection to AIDS, γ, leads to an exponentially decaying distribution of time from infection to AIDS, $c(t) = \gamma e^{-\gamma t}$. But the data shows that $c(t)$ gradually increases for the first 6-10 years after infection, and a Weibul distribution $c(t) = mt^n e^{-mt^n}$, with $n = 2.4$ and $m = 0.11$ is a good fit to current data. There is some evidence that infectivity may vary with disease stage, with a short infectious period early in infection, a long noninfectious period, and then people becoming more infectious the closer they get to AIDS. There is a large variation in behavior, even among homosexual men. Some men have very many partners and some have few: if we examine the distribution of men according to numbers of partners in some time interval, we see that the variance is large compared to the mean squared, with the distribution decaying roughly as p^{-n}, n about 3 or 4, for p large. Similar distributions presumably hold for heterosexual people and for intravenous needle-sharing. The transmission rates for different sex acts may be different, age may play a strong role in how people choose partners, and who they choose, distance may be important, etc.

Noting that the high variance to mean-squared ratio in the numbers of partners implies that this is an important variable, Anderson, et al.[2] introduced the notion of distributing the population according to the partner change rate, r. Thus susceptibles now become a population density, $S(t, p)$, etc. To account for the time from infection to AIDS, they distributed the infected population according to time from infection to AIDS, τ, giving $I(t, \tau, p)$, which has the units people per partner/year per year (people per partner). AIDS cases can similiarly be distributed by time since AIDS, which we also designate τ, giving $A(t, \tau, p)$. Note that this is somewhat confusing notation: $S(t)$ is the integral over p of the density $S(t, p)$; $I(t, p)$ is the integral of $I(t, \tau, p)$ over τ; etc.

As soon as we introduce the distribution of people according to risk, we have to start worrying about how people mix. This problem would also arise if we introduced sex, age, type of contact, distance, etc. The age/sex problem is a classical problem in fertility analysis (how are marriages distributed, who makes the partnering choice). There are two obvious extremes that we can talk about: people choose their partners solely based on availability, with no regard to who they are; and people choose partners who are identical to themselves. Reality, of course, lies in the middle, and there may, under some circumstances, even be a bias of high and low for each other (for example, with prostitution).

Determining contact patterns becomes a difficult mathematical task in itself: a couple of constraints must be satisfied. When a person with risk p has a partner with risk q, the opposite must also happen. A person with p partners per year should have p partners per year. A person must have a nonnegative number of partners from all groups.

If $\rho(p,q)dq$ is the fraction of partners of a person with p partners per year that have between q and $q + dq$ partners per year (ρ is a probability density function), then the constraints on ρ are

1. when a person with risk p has a partner with risk q, the reverse must happen, or $\rho(p,q)pN(p) = \rho(q,p,)qN(q)$, where $N(p)dp$ is the total number of people with risk between p and $p + dp$,
2. the rate of partner choice of a person should be the value specified, or

$$\int_0^\infty \rho(p,q)dq = 1 ,$$

and

3. $\rho(p,q)$ is strictly positive.

Although satisfying these constraints will not give a unique result, it is non-trivial to find families of $\rho(p,q)$ that satisfy all three constraints. Anderson, et al.[2] chose to assume random partner choice, for which these constraints can be easily satisfied. Colgate, et al.[7] postulated the otner extreme, which just gives independent epidemics. I have developed a family of solutions to this mixing problem, which allows a fairly wide range of mixing to be specified. It is based on the assumption that there is a way of ordering the population in terms of desirability, and has both of these extreme cases as limiting possibilities. If this ordering goes from lowest risk to highest risk, then those of lowest risk decide how their partners will be distributed among all risk groups based on availability, $qN(q)$, and acceptability, normalized by the availability and acceptability of all possible partners. The partnerships chosen by this group are removed from circulation using the symmetry constraint (1.) and then the next lowest risk group chooses partners from themselves and all groups at higher risk than themselves. This formulation, which satisfies all three constraints, is

$$\rho^{ordered}(p,q) = \begin{cases} \rho(q,p)qN(q) & \text{for } q > p \\ (1 - \int_0^p \rho(p,x)dx)\frac{f(p,q)qN(q)}{\int_p^\infty f(p,x)xN(x)dx} & \text{for } q \geq p \end{cases} \qquad (3a)$$

$f(p,q)$ is an arbitrarily chosen acceptance function. There is nothing particularly special about the lowest group; we could use any ordering that we want. By choosing different acceptance functions, we can mimic a large range of mixing patterns. If $f(p,q) = 1$ then we recover proportionate mixing, while if $f(p,q)$ is a narrow function such as $e^{-(p-q)^2/\epsilon(p+q)^2}$ then self-selection occurs. Once we have any set of formulations of $\rho(p,q)$ we can take a linear combination of them, with coefficients that add up to 1, and still satisfy the three constraints.

This then can be put into $\lambda(t,p)$, which now becomes

$$\lambda(t,p) = p\int_0^\infty k(t,p,q)\rho(t,p,q)dq \text{ , where} \qquad (3b)$$

$$k(t,p,q) = c(p,q)\int_0^\infty i(r)\frac{I(t,r,q)}{N(t,q)}dr . \qquad (3c)$$

We then obtain a system which is a modified version of (1):

$$\frac{\partial S}{\partial t} = \mu(S_o(p) - S(t,p)) - \lambda(t,p)S(t,p) \ , \tag{4a}$$

$$I(t,0,p) = \lambda(t,p)S(t,p) \ , \tag{4b}$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial \tau} = -(\gamma(\tau) + \mu)I(t,\tau,p) \ , \tag{4c}$$

$$A(t,0,p) = \int_0^\infty \gamma(\tau)I(t,\tau,p)d\tau \ , \tag{4d}$$

$$\frac{\partial A}{\partial t} + \frac{\partial A}{\partial \tau} = -\delta(\tau)A(t,\tau,p) \ . \tag{4e}$$

Note that now people become infected (or develop AIDS) at $\tau = 0$ and convect along one year of infection (or AIDS) for each year of time.

What does this complicated system mean? It is possible to make some estimates for the situation of initial growth of the epidemic. First note that the virus is spreading much faster than people are developing AIDS or than the population is being replenished. In other words, μ and $\gamma(\tau)$ are small compared to icp, at least for the first several years, and we can neglect birth/death terms. Now, suppose that mixing is very narrow and given by the above exponential, with ϵ very small. As $\epsilon \longrightarrow 0$, asymptotic analysis of integrals can be used (Laplace's method) to see that

$$\lambda(t,p) \longrightarrow p[k(t,p,p) + \frac{\epsilon}{2(p+a)pN(t,p)}\frac{\partial}{\partial x}((x+a)^2 xN(t,x)\frac{\partial k(t,p,x)}{\partial x})]_{atx=p} \ ,$$

to $O(\epsilon)$. If we then also take $c(p,q)$ and $i(\tau)$ to be constants, and $N(p)$ to be $N_o p^{-n}$ for p large, we obtain a very simple diffusion equation for the number infected:

$$\frac{\partial I(t,p)}{\partial t} = \frac{ic}{N_o}(N_o p^{-n} - I(t,p))p[p^n I(t,p) + \frac{\epsilon}{2}p^{n-2}\frac{\partial}{\partial p}(p^{3-n}\frac{\partial p^n I(t,p)}{\partial p})]$$

for large p and small ϵ. This equation has similarity solutions which are waves moving from high risk to low risk of the form $p^n u(pt)$. The total number infected then grows as t^{n-1}, which is very interesting. Most epidemics grow exponentially, at least at first, but this one has grown in a polynomial fashion from very early on (AIDS cases have grown as t^3)[7]. So this model provides a plausible explanation for this growth.

A typical simulation with the full model is shown in Figure 2. The effect of varying the mixing function is shown in Figure 3. Note that as mixing gets wider there is less and less of a sharp wavefront. The growth also become more exponential. Note that the epidemic also eventually decimates the sexually active population, despite continuous replenishment. This is plausible, but not necessarily correct.

We must be very careful about the quantitative predictions - too many of the parameters are too poorly known, and we have neglected a large number of

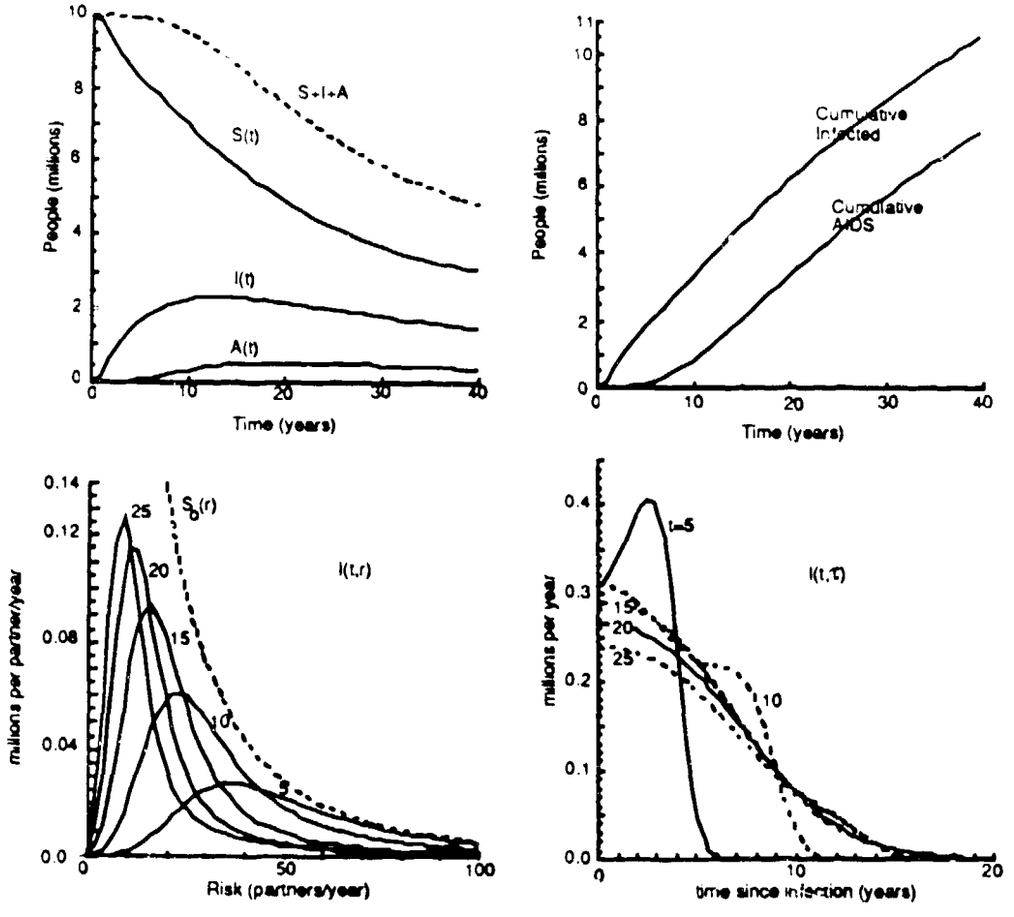

FIGURE 2 A typical calculation of the model in Eq. 4, with a variable infectivity, fairly narrow mixing function, and one contact per partner. Upper left: changes in each population over time. Upper right: total numbers ever infected or with AIDS. The increase in both populations is roughly polynomial, with a power between 2 and 5, for the first 10 years. Lower left: infections distributed over risk every 5 years. Lower right: infections distributed over τ every 5 years.

characteristics that isolate people socially. A more detailed discussion of this model and the parameter choices, along with more simulations, can be found in Hyman

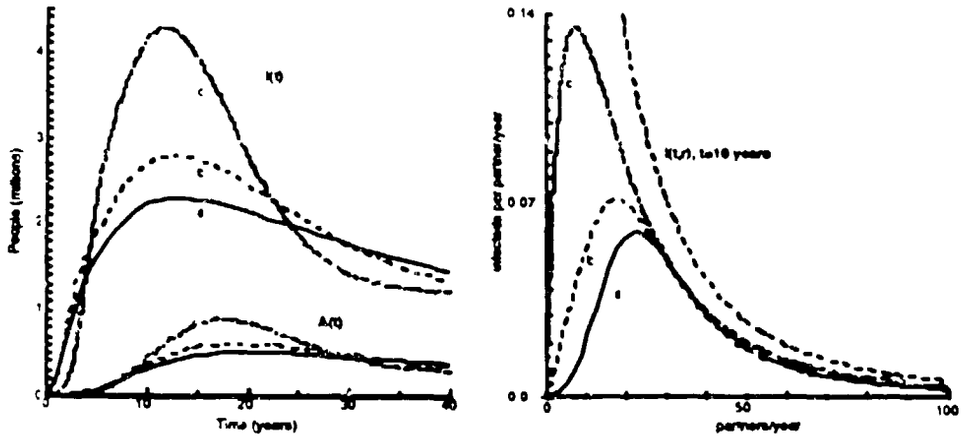

FIGURE 3 What happens as the mixing width increases. (a) same as in figure 2. (b) f(p,q) twice as wide. (c) random mixing. The epidemic gets faster and reaches lower risk groups much earlier the greater the mixing.

and Stanley[15,16].

DISCUSSION

I have presented several models of the AIDS epidemic. These models are simplified. They neglect age structure, spatial heterogeneities, the difference between sexes, contact-type, etc. But we can learn much about the mechanisms behind the disease spread from these simple models. We can see that the nonexponential growth of this epidemic is probably due to population structure and the contact networks within this structure. Different models can and will answer different questions. This is a field in which there is a flurry of research that is likely to revolutionize our approach to modeling infectious diseases. It will also change the way that parameters, such as infectivity, are measured. But many puzzles remain, and much work can still be done.

Most of the work on AIDS modeling is very recent, and the papers on the subject, other than those already cited, are still in press. Exciting papers that will soon appear include a couple by a group at the University of Michigan that are very concerned with mixing questions[17,18], a more theoretical paper on time delays by Castillo-Chavez, et al.[6], and a paper that examines the question of replacing

the continuous distribution with a small number of risk groups, asking how can we choose the groups optimally, by Blythe and Anderson[5]. A paper by May, et al.[21], starts to look at the question of age-structured models and their implications.

Models of the immune system, on many levels (cellular, systemic), could also be extremely useful to help provide a structure to the confusing bits of information that are being assembled. Little work has been done to date, possible because the information has been so confusing, so this is a field that is wide open for discovery.

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