YEARBOOK OF PHYSICAL ANTHROPOLOGY 33:245–276 (1990)

Modeling the Spread of Infectious Disease in Human Populations

LISA SATTENSPIEL
Department of Anthropology, University of Missouri, Columbia, Missouri 65211

KEY WORDS Mathematical model, epidemiology, influenza, malaria, HIV, AIDS

ABSTRACT For the past 20 years, there has been an epidemic associated with the development of mathematical models to describe the spread of disease. This epidemic shows no signs yet of dying out. Four major topics related to this discipline are discussed here, including the following: 1) an introduction to the basic assumptions and general framework common to most epidemic models; 2) a discussion of the major questions addressed by epidemic modelers; 3) a brief outline of several of the approaches used in the development of disease models; and 4) reviews of models that have been developed for influenza, malaria, and AIDS. The utility of these models and suggestions for contributions that anthropologists can make to this field are also discussed.

Over the last few decades, the number of models developed to describe the spread of disease has been rapidly increasing. In 1975 Norman T. J. Bailey published the second edition of his classic review, *The Mathematical Theory of Infectious Diseases*. The bibliography of this book documents 539 articles on mathematical epidemiology written between 1900 and 1973. Of these 539 papers, 336 (62%) were published between 1964 and 1973. The distribution of these papers by year is given in Figure 1 and looks remarkably like the beginning of an epidemic curve for a disease that is not transmitted easily, but that spreads rapidly once there is a critical number of infected individuals. Extrapolating this curve to include the years from 1974 to 1989 gives one an idea of the quantity of papers now to be found that incorporate some aspect of the development or analysis of mathematical models for disease spread.

To avoid updating and expanding Bailey's 1975 monograph, this paper will review only models addressing the spread of human disease. However, because of the volume of these papers, only a select portion of the literature on human epidemic models will be included. First, there will be a discussion of the important biological and social factors that may be incorporated into epidemic models. Second, there will be an overview of the major questions leading to the development of epidemic models. This will be followed by a review of the major approaches to the modeling of infectious diseases. Finally, applications of these approaches to three diseases—malaria, influenza, and AIDS—will be considered. The models developed for these diseases and the application of these models to actual populations contain much of interest to anthropologists.

INTRODUCTION TO EPIDEMIC MODELS

Infectious diseases are transmitted as a result of direct or indirect contact between an infectious person and a susceptible person. Consequently, models for the

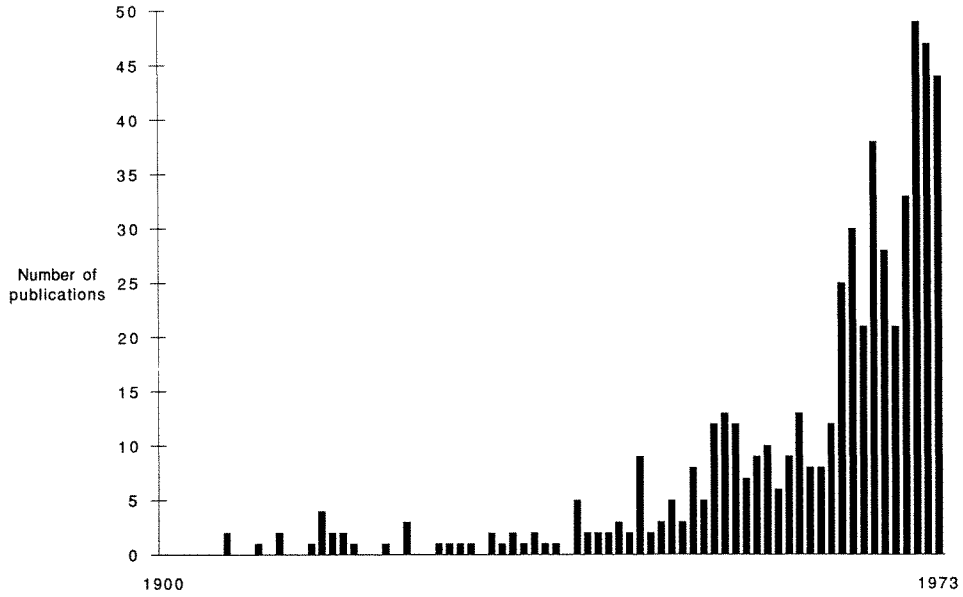

Fig. 1. Number of publications concerned with mathematical models for contagious processes that are cited in Bailey (1975). Data include articles or books published from 1900 to 1973 by year of publication.

transmission of infectious diseases in human populations must consider at least these two types of individuals. The population size is usually assumed to be a constant, N, so that $S + I = N$, where S is the number of susceptible individuals and I is the number of infective individuals. Many models also assume that there is no migration and that there are no births or deaths in the population. Because of the nature of disease transmission, most epidemic models begin by looking at the rate of contact between susceptible and infective individuals.

The simplest model (called the *SI model*) was developed for diseases spread by direct human-human contact and considers a population composed only of individuals who are either susceptible or infective. The model assumes that there is no recovery from the disease and that there is random mixing among individuals within the population. It is based on the principle of mass action, which was first proposed in the context of epidemiological models by Hamer (1906) and later elaborated by Ross (1915), Kermack and McKendrick (1927), and Soper (1929). This principle is a consequence of the assumption of random mixing. In mass-action models, the number of new infections is simply βSI, the product of the number of susceptibles and the number of infectives (which gives the total number of contacts between a susceptible individual and an infective individual) times the infection rate, β, which is the proportion of contacts that results in infection. As there is no recovery once an individual is infected, there is no change in status. This process can be described by the differential equation

$$dS/dt = -\beta SI = -\beta S(N-S)$$

where S and I are the number of susceptible and infective individuals in the population and β is the proportion of contacts between susceptibles and infectives that result in transmission of the infection. A complete solution of this model is given in Bailey (1975). Results of the analysis show that eventually all individuals in the population become infected.

A number of models consider an alternative to the mass action principle called the *Reed-Frost formulation*. This formulation was derived by Lowell Reed and

Wade Hampton Frost in the late 1920s but was not published until the early 1950s (Abbey, 1952; Maia, 1952). Dietz and Schenzle (1985) and Dietz (1988d) point out that it was also derived independently by E'nko (1889). In this model, the transmission of infection is defined in terms of a "probability of effective contact" rather than a proportion of contacts that result in transmission. Effective contact is the type of contact necessary for transmission of infection, not necessarily just casual contact.

The Reed-Frost formulation considers the likelihood that a susceptible individual will escape infection within a given period. Let p be the probability of effective contact per infective individual. Then $1 - p$ is the probability that a given susceptible does not come into contact enough with one infective to contract a case of the disease. In order to escape transmission altogether, the susceptible must not have adequate contact with any of the cases in the population. In a randomly mixing population, the probability of contact with one case is independent of the probability of contact with another case. Thus the probability of avoiding contact with all cases at time t, C_t, is $(1 - p)^{C_t}$. The probability that the infection is transmitted to a given susceptible individual is then $1 -$ {the probability that the susceptible escapes transmission from all cases} or $1 - (1 - p)^{C_t}$. The expected number of new cases is this probability times the number of susceptibles in the population. The Reed-Frost model can thus be represented by

$$E[C_{t+1}|\, C_t, S_t] = S_t\{1-(1-p)^{C_t}\}.$$

The number of new cases has a binomial distribution, since in any one contact there is or is not transmission. Therefore, the probability of obtaining $C_{t+1} = x$ new cases given C_t and S_t is

$$P[C_{t+1} = x|\, C_t, S_t] = \binom{S_t}{x}\{1-(1-p)^{C_t}\}^x\{(1-p)^{C_t}\}^{(S_t-x)}$$

The consequence of this formulation is that models based on it are generally more probabilistic in nature. They explicitly consider chains of contact among individuals rather than diffuse interactions among the individuals within a population or among subgroups of a population, and they take into account that there are chance factors involved in the transmission of the infection.

Jacquez (1987) points out a problem with the internal consistency of the formulation of the Reed-Frost model. He shows that an internally consistent Reed-Frost type model can be formulated, but that the assumptions about the probabilistic process required for this model are clearly unreasonable. He presents a model derived through the use of E'nko's model and the use of generating functions that does not have the inconsistencies of the Reed-Frost formulation, but that retains the basic approach of the model.

Both the mass-action and Reed-Frost approaches are common in mathematical epidemiology. Generally, the more mathematically inclined researchers prefer the mass-action approach, whereas more statistically inclined researchers prefer the Reed-Frost approach. A Reed-Frost approach is probably better for small populations because of the random effects built into the model, but Reed-Frost models are also more difficult to analyze. The ultimate choice of model invariably will depend on both the modeler's background and the focus of the model.

There are a number of problems with these simple formulations. First, they are not appropriate for diseases that are not spread by direct human-human contact. However, at least for diseases with human–vector–human transmission, a mathematical term consisting of some transmission function multiplied by the product SI can be built into a mass-action formulation. Most of the biological factors associated with the vector species can be incorporated into the transmission function.

A second problem with the simple formulation of the transmission from infective to susceptible derives from the assumption of a large randomly mixing population. Most early epidemic models were developed by mathematicians who did not have

efficient computers available and who therefore were concerned with the development of models that were analytically tractable. Random mixing among individuals was one assumption that simplified the models enough to allow reasonable results and intuitions. However, real populations do not mix randomly.

Although a few models incorporating nonrandom mixing were developed earlier, the biggest push toward the development of such models began in the mid-1970s with the work on sexually transmitted diseases by Cooke and Yorke (1972, 1973), Lajmanovich and Yorke (1976), Yorke et al. (1978), Nold (1980), Hethcote et al. (1982), and Hethcote and Yorke (1984). These models were developed in response to an increasing incidence of sexually transmitted diseases (especially gonorrhea) in the United States and used to aid in the development of control measures for gonorrhea.

The nature of sexual transmission makes the assumption of one large, randomly mixing population patently unrealistic. At the very minimum, sexually transmitted disease models require a simple structured population divided into two groups, males and females, since there is differential contact within and between the sexes. The gonorrhea models also included the concept of core and noncore groups that varied in their level of sexual activity. Mixing within groups was assumed to be random, while mixing between groups was assumed to occur at rates proportional to the sexual activity levels of the groups involved.

In the last 3 years, a large number of models have been developed for another sexually transmitted disease: AIDS. Because of the nature of transmission of the disease, virtually all models that have been developed to describe the spread of AIDS have considered structured, nonrandomly mixing populations. These models will be reviewed in detail below.

In addition to the models for the spread of sexually transmitted disease, structured models have been developed to describe the spread of measles (Haggett, 1972, 1976; Cliff et al., 1975, 1981), influenza (Baroyan et al., 1977; Rvachev and Longini, 1985; Longini, 1988), smallpox (Travis and Lenhart, 1987), and hepatitis A (Sattenspiel, 1987; Sattenspiel and Simon, 1988). Andreasen and Christiansen (1989) extend the theoretical analyses of the effects of population structure, although they do not apply their results to any specific disease. These models have arisen in response to the recognition that virtually all human populations are structured in some way, so that the assumption of random mixing among individuals within the population is rarely appropriate for any disease.

A number of models have also considered the influence of age structure of a population (for example, Anderson and May, 1985; Castillo-Chavez et al., 1989e; Dietz, 1982; Dietz and Schenzle, 1985; Hethcote, 1988). Because humans tend to interact with people of similar age far more often than would be expected under conditions of random mixing, the consequences of age structure are similar to the consequences of other types of population structure.

A third problem of the simple epidemic models is that they lead to highly unrealistic epidemic patterns. Since all individuals in the population can become infected and since there is no recovery from the disease and no influx of new susceptibles through birth or migration, *SI* models lead to a situation in which all individuals in the population are infected. This behavior occurs rarely, if at all, in the real world.

Because of this, models for most diseases include at least one or two additional stages. The most common extension to the simple *SI* model is to include recovery from the disease. Recovery usually is assumed to occur at a constant rate, γ, proportional to the number of infective individuals in the population. Models with recovery are frequently called *SIR models*. The complete solution to the simplest *SIR* model has been presented in Bailey (1975). Results from the analysis of this model show that there is a critical population size of susceptibles required for an epidemic to occur. If the initial number of susceptibles is below this number, then the disease will immediately die out. If the initial number of susceptibles is above this number, there will be an epidemic of the disease until enough susceptibles

have been infected to reduce the susceptible population to a level below the critical size. Following this, the disease will die out. In either case, the disease eventually goes extinct in the population.

Another common addition to epidemic models is to consider a latent period for the infectious organism. This is a stage *after* infection, but *before* the infected individual becomes infectious and can transmit the disease. Models including the latent period are usually called *SEIR models*, with the *E* standing for *exposed.* Many models assume that the latent period is negligible, but this assumption is not appropriate in all cases. The purpose of the model, the background rate of mortality in the population, the length of the latent period, and other similar factors will influence the decision to incorporate the latent period.

Another problem with the simplest *SI* models (and also with many *SIR* and *SEIR* models) is that they do not explain the maintenance of diseases at an endemic level or the recurrence of epidemics over time. In order to have either of these situations, there must be a continual influx of new susceptibles to replace those that have become infected. Otherwise, the susceptible population will become depleted and the chain of transmission will be broken, resulting in extinction of the disease. The influx of susceptibles can occur in a number of ways, including births, migrations, and loss of immunity. Realistic models for most diseases must include one or more of these factors.

Because of the conditions mentioned above, most disease models are based on the following model:

$$S \xrightarrow[\text{transmission}]{} E \xrightarrow[\text{latency}]{} I \xrightarrow[\text{recovery}]{} R \xrightarrow[\text{loss of immunity}]{} S$$

Different models will consider various stages, depending on the disease in question and may or may not consider vital statistics. Models will also vary with regard to the complexity of the formulation of the transitions, especially with regard to the transmission probability. Generally, the particular formulation used depends on the question addressed by the model. The next section describes some of the more common questions considered by disease modelers.

MAJOR QUESTIONS OF INTEREST TO EPIDEMIC MODELERS

A majority of disease models developed prior to 1980 were formulated by applied mathematicians. Because of this, the major questions addressed by models had to do with the qualitative behavior and analytical solutions of the models. Mathematical epidemiologists were concerned with whether or not and under what conditions an epidemic would occur and when a disease would be maintained in a population. Another major consideration was how the system behaved at equilibrium given a particular set of starting conditions.

Some important insights into the behavior of diseases in human populations derived from these methods, the most important being the concept of a threshold for the development of an epidemic. This threshold is a critical population size above which an epidemic will develop and may be maintained if there is a sufficient influx of new susceptibles through birth, migration, or loss of immunity. If the population size is below the threshold, then the disease will die out and cannot be maintained. Analysis of a variety of models results in the identification of an appropriate threshold.

Bartlett (1960) and Black (1966) attempted to use the results of mathematical models to estimate critical population sizes necessary for the maintenance of measles in a population. Bartlett estimated that 250,000–300,000 people are needed for the maintenance of measles in United States cities, whereas Black estimated from data on measles incidence in a group of Pacific islands that about 500,000 people are required. In smaller populations, there is not a large enough influx of new susceptibles to maintain the chain of transmission.

In spite of the descriptive and practical value of Barlett's and Black's work, the

majority of results from the mathematical analysis of epidemic models have been of much more interest to mathematicians than to epidemiologists. However, this situation has changed significantly in the last 10 years. Although much of mathematical epidemiology continues to consist largely of mathematical analysis, there has been a growing interest in the validation of models using data from actual disease epidemics.

A number of factors have been important in the shift toward linking epidemic models to real situations. These include the development of faster and better computers to allow for complex simulations of disease spread, an increased interest of population biologists in the dynamics of host-parasite and, more specifically, human-parasite interactions, and a greater acceptance of interdisciplinary projects, especially in biomedical fields. In addition, since the development of the gonorrhea models in the late 1970s and early 1980s, many models for disease spread have emphasized the problem of evaluating possible control measures for diseases rather than qualitative mathematical analyses. A discussion of the value of mathematical models for developing and evaluating control measures for measles, malaria, and AIDS is presented in Aron (1988b).

As a consequence of this shift in emphasis, instead of being an area of concern primarily to applied mathematicians, mathematical epidemiology now has a variety of proponents from within the fields of biology, epidemiology, statistics, and the social sciences, as well as mathematics. These fields have long emphasized the importance of data (sometimes to an extreme), with the result that recent studies are more concerned with combining epidemiological data and models in meaningful ways.

One consequence of the joint consideration of data and models and the corresponding emphasis on policy decision with regard to control measures is that there has been a shift in emphasis away from the idea of an epidemic threshold in favor of a concept called the *basic reproductive rate,* or R_0. R_0 is the number of secondary infections produced by one primary infection in a totally susceptible population. The epidemic threshold, ρ, for the simple *SIR* model can be shown to be equal to γ/β, where γ is the recovery rate, and β is the transmission rate (Bailey, 1975). R_0 is equal to $\beta S_0/\gamma = S_0/\rho$, where S_0 is the initial population of susceptible individuals (Murray, 1989).

The traditional threshold condition is expressed in terms of a relationship between S_0 and ρ. If $S_0 > \rho$ the disease persists; if $S_0 < \rho$ the disease dies out. Because $R_0 = S_0/\rho$ the condition $S_0 > \rho$ is equivalent to the condition $R_0 > 1$. Similarly, the condition $S_0 < \rho$ is equivalent to the condition $R_0 < 1$. However, the R_0 conditions differ slightly from the S_0 conditions in their interpretation. If $R_0 > 1$, then each infectious individual will pass the infection to more than one susceptible individual. Thus, the disease can be maintained in the population. If $R_0 < 1$ then the disease will die out in the population because it is not able to reproduce itself at a sufficient rate. The epidemiological R_0 is thus analogous to the R_0 used in demographic studies of population growth.

One advantage of R_0 over ρ is that the emphasis shifts from overall population size to a measurement of the number of additional infections that one infectious individual must generate. This kind of information is frequently collected or estimated by epidemiologists, and thus R_0 has proven to be a more useful concept for practicing epidemiologists who are concerned with how best to determine effective control measures. The epidemiologists need only consider how to break the chain of infections fast enough to guarantee that an infectious individual gives rise to no more than one secondary infection; they do not need to worry about how to make a (usually growing) population smaller so that there will be an insufficient number of susceptible individuals. The fact that breaking the chain of infectives at a rate such that $R_0 < 1$ is equivalent to decreasing the *effective* population size to a level predicted by ρ is a subtlety that might not be appreciated by many epidemiologists.

Another question of interest in addition to the mathematical analysis of epidemic models and the evaluation of control measures is the patterns of disease

spread in human populations. This question has been considered at both the household level and at the level of geographic region. Much of the work on household spread has been done by Longini and colleagues (Longini and Koopman, 1982; Longini et al., 1982, 1984; Haber et al., 1988) and by Becker (1981). These studies were motivated by a desire to separate household sources of infection from community sources of infection when the data were collected in observational studies. These methods result in more effective ways to use serological data to analyze the social and environmental determinants of transmission.

Much more work has been done on the question of geographic spread of disease, and this is one of two topics that is of most interest to anthropologists. A number of speculative papers have been written on the importance of disease during various stages of human evolution (for example, Armelagos and Dewey, 1970; Black, 1975; Cockburn, 1971), although these usually do not include any attempts at modeling. There is also an increasing number of papers devoted to discussions of the influence of disease on native New World populations, but only a handful make attempts at using models (Milner, 1980; Ramenofsky, 1987; Upham, 1986) and the use of models in these papers is not very sophisticated.

McGrath (1988) made more extensive use of mathematical models in her study of the spread of tuberculosis in the lower Illinois valley. She addressed the issue of the importance of social networks for the spread and maintenance of disease and found that effective population size was most likely the critical factor determining maintenance or extinction of tuberculosis in these populations.

There have been a number of studies looking at the spread of disease among island populations. Black's (1966) work on the effects of island population size on the likelihood that a disease would remain endemic has been discussed above. There are also a number of papers on the spread of measles in Iceland and the British Isles (Cliff et al., 1981; Cliff and Haggett, 1980, 1984; Cliff and Murray, 1977; Haggett, 1982). These studies look at the problem of epidemic spread in a semi-isolated island population, a setting that has long been of some interest to physical anthropologists and population geneticists. The models pay close attention to the influence of population structure and social interactions on the patterns of disease spread and use a combination of standard geographic analysis and epidemic modeling.

A second question of particular interest to anthropologists is the effect of infectious diseases on the demographic structure of a population. There have been a number of historical epidemiological studies of the spread of smallpox on the Åland Islands, Finland, and on the Finnish mainland during the 18th and 19th centuries (Jorde et al., 1989a,b; Mielke et al., 1984; Pitkänen et al., 1989). These papers analyze the effects of smallpox on the demographic structure of these populations both before and after the widespread use of vaccination. Mercer (1985) has also considered the demographic impact of smallpox vaccination in Europe. Meegama (1986) has studied the effects of malaria control on mortality reduction in Sri Lanka after World War II. Anderson et al. (1988), Bongaarts (1989), and May et al. (1988, 1989) have considered the impact of AIDS on the demographic structure of a population. Aron and Sarma (1989) use life table analysis in their model to examine the effect of demographic structure on the risk of HIV spread among heterosexuals in the United States. Because of the importance of infectious disease as a cause of morbidity and mortality in all human populations and the paucity of studies looking at disease as a demographic factor, this is an area ripe for future studies and attention from anthropological demographers.

APPROACHES TO THE DEVELOPMENT OF INFECTIOUS DISEASE MODELS

A number of approaches have been used in the development of models to address the questions discussed above. These approaches include four types: 1) compartment models, 2) statistical approaches, 3) geographic approaches, and 4) economic models.

The most common method in use is compartment models, an approach advocated

and aptly described for epidemic models by Bailey (1975). The *SI*, *SIR*, and *SEIR* models discussed above fall into this category. The models consist of a number of compartments based on the disease status (*S,E,I,R*, etc.) of an individual. Individuals pass or flow from one compartment to another as they progress in the disease. Rate parameters such as β, the transmission rate, and γ, the recovery rate, determine how long an individual stays in a compartment. Models of this type have been used in studies focused on all the questions discussed above.

The compartment models are mathematical models for the spread of disease. The process of building a mathematical model begins with a series of assumptions about how the disease process works and the development of a simplified model to describe the process. As a consequence of analysis of the initial model, comparison with actual disease data, and evaluation of the assumptions, the model is reformulated in a more realistic manner. In general, the process of mathematical modeling proceeds from simple to complex.

A statistical approach, on the other hand, begins with all that is known about a system and attempts to find a model that will best fit the data. Statistical models attempt to identify a few or several parameters that can be used to describe a system rather than all existing data. Often the functional relationships involved are unknown, but the hope is that the process of model development and analysis will result in general understanding of the way a system works rather than simple description of observed results. The process of statistical modeling thus proceeds from the complexities of the real world to something that is easier to understand.

In order to get the best understanding of the consequences of an epidemic, both types of approaches should be considered together. Unfortunately, this is rarely the case. Mathematicians and statisticians are often interested in very different questions, and it is rare for them to attempt to come together on common ground.

The use of statistical modeling is a more traditional approach in epidemiology than is the use of mathematical modeling. A review of this area is beyond the scope of this paper. However, there are three areas that are of more general interest to anthropologists. The first includes attempts to combine statistical parameter estimation with the development of mathematical models. Statistically based epidemic models are usually built upon a Reed-Frost epidemic model rather than a mass-action model. Examples of this approach include studies on household distribution of diseases by Longini and Koopman (1982) and Longini et al. (1982, 1984) and HIV models developed by Morris (1989) and Longini et al. (1989). These authors combine compartmental type models for disease spread with sophisticated statistical modeling to estimate the values of the parameters used in their models.

The studies of historical epidemiology on the Åland islands and the Finnish mainland by Jorde et al. (1989a,b), Mielke et al. (1984), and Pitkänen et al. (1989) have also used some interesting statistical modeling to analyze disease data. Methods used include time series analysis to determine if there is significant cycling of disease mortality and statistical analyses to determine seasonality in smallpox deaths. These and other analyses are used to assess the relative importance of smallpox and the introduction of vaccination for the disease on the demographic structure of the populations.

Shaffer and Kot (1985, 1986) have applied concepts and techniques for the study and detection of chaotic systems to patterns of spread of infectious diseases. They find that observed data on measles in Baltimore and New York City exhibit certain "fieldmarks" of low-dimensional chaotic systems and cannot be described as effectively with purely stochastic models. Chickenpox and mumps, on the other hand, cannot be described by low dimensional chaotic systems.

A large amount of work on the spatial diffusion of epidemics has been done by geographers using approaches that differ from those used for other questions. Some of the geographic studies are based on the analysis of maps giving the spatial and temporal distribution of cases of a disease (Angulo, 1987; Angulo et al., 1979, 1980). Most non–map-based geographic approaches are based on a mathematical diffusion model and assume that the disease spreads in all directions from an

initial focus through a population that is distributed homogeneously or heterogeneously over a region (for example, see Cliff et al., 1981).

Other ways to approach geographic spread include the use of contact models, in which contact between individuals occurs on the basis of some underlying function that may or may not be directly related to the geographic distance between individuals, and the use of multiple-site models, in which the population is divided into two or more subgroups within which mixing is assumed to be random, but with reduced interaction between subgroups. Examples of contact models include Kendall (1965), Daniels (1975), and Diekmann (1978). For recent overviews of multiple-site models, see Sattenspiel and Simon (1988) or Sattenspiel (1989).

The fourth major approach to epidemic modeling, economic models, is concerned primarily with assessing the appropriateness of particular control methods. Many compartmental models (especially an increasing number of newly developed models) are also concerned with the development of appropriate control strategies. The compartmental models usually consider how different control measures affect R_0 and attempt to determine appropriate strategies to guarantee that $R_0 < 1$. Economic approaches are quite different.

The earliest models of this type considered methods to control tuberculosis (Brøgger, 1967; Feldstein et al., 1973; ReVelle et al., 1967; ReVelle and Male, 1970; Waaler, 1968; Waaler and Piot, 1969). These studies are based on a difference equation model with random mixing, prophylaxis, and vaccination. Linear programming methods were used on an optimization model derived from the descriptive model to determine the best way to allocate resources to treatment and control of tuberculosis.

A number of studies have considered cost-benefit analyses of different control strategies, especially vaccination, for particular diseases (Koplan et al., 1979; Schoenbaum et al., 1976a,b; Willems and Sanders, 1981). This approach does not consider explicitly the dynamics of disease spread; attention is given only to the economic costs and benefits of various control measures.

MODELS FOR SELECTED DISEASES

It is obvious from the discussion so far that there are a number of different questions to consider and approaches to use. To see better how these are applied, the remainder of this review will look at models that have been developed for three particular diseases: influenza, malaria, and AIDS. These diseases have been chosen because of their likely interest to anthropologists.

Most mathematical models for the spread of influenza are concerned with the global spread of the disease, spread within small communities, or spread within the household, and focus on the consequences of human social interactions for disease spread. Studies on global spread have considered the importance of transportation networks as a mechanism carrying infective individuals all over the world. Household studies concentrate on interactions among individuals at the family level. In both of these types of studies, human interactions are not explicitly included. However, the small community studies for influenza transmission incorporate many levels of human interaction and have been moderately successful in predicting patterns of disease spread. These models will be discussed further below.

There are numerous anthropological studies looking at interrelations between malaria, sickle cell anemia, and the development of agriculture in equatorial Africa. There is an equally large, or larger, body of literature on mathematical models for the transmission, control, and eradication of the disease. Most of these models are strictly biological in approach; there is thus much room for the incorporation of cultural and behavioral factors by anthropologists.

Models that have been developed to study the spread of HIV and AIDS are also reviewed. Because the disease is spread as a consequence of some of the most intimate of human behaviors, many of these models have focused on human behavioral interactions and their importance for disease spread. Very interesting and

difficult problems have to be faced when trying to determine ways to model human sexual behavior and other high-risk behaviors. Most studies to date have focused on the problem in the developed world, but the methods that are being devised will be of considerable value in studies of the disease in other parts of the world. There is abundant room in this area for anthropologists with their interest and understanding of other cultures.

Influenza

Fine (1982) characterizes influenza as "the last great plague" because it "probably has a greater impact upon the health of developed countries, in terms of morbidity, mortality, and economic disruption, than does any other single infectious disease." It is a clinical illness associated with infection with a member of a group of RNA viruses—the myxoviruses—which are found in a number of different animal species. Those capable of causing clinical illness in humans are categorized as type A, B, or C, depending on the specific nucleocapsid antigen they contain. Most of the modeling work concentrates on the transmission of type A influenza.

One of the major problems associated with influenza control is rapid evolution of the viruses. There are two major antigens associated with the viruses, haemagglutin (H) and neuraminidase (N). Periodically there may be major "shifts" in either of these two antigens or minor "drifts," which occur more frequently than the shifts. Generally, antigen drift does not lead to clinical illness in people who have already been exposed to the antigen that has drifted. Drift usually can be ascertained only by serological tests. Antigenic shifts result from more extensive changes in the antigens, and usually there is little or no effective cross-immunity in an individual from previous exposure to similar antigens.

Different combinations of H and N antigens result in different strains of the virus. For example, "Asian" flus are H_2N_2 viruses, whereas "Hong Kong" flus are H_3N_2. There are significant differences in the epidemiological behavior of different strains, some of which may be explained by the history of past exposure in a given population and resulting differences in antibody prevalence, and some of which are likely explained by differences in virulence or pathogenicity. Even though there are significant epidemiological differences, most transmission models do not take these differences into account. The focus of the models is more on understanding the dynamics of the contact between individuals rather than the consequences of antigenic variation in the virus.

There are a number of epidemiological factors included in models of transmission of influenza. First, many diseases have a significant *latent period,* which is the time from infection to the time when an infected individual becomes infectious. This is not the same as the *incubation period,* which is the time from infection to the development of symptoms, but most models for the transmission of influenza assume that the two are the same. Because influenza has been estimated to have a short incubation period of from 24 to 72 hours with a lognormal distribution (Sartwell, 1950; Moser et al., 1979), this assumption is not likely to lead to much error in the models.

A second epidemiological factor is the length of the infectious period. This period is highly variable, both within a population experiencing an outbreak of the disease and among outbreaks of different strains of the disease. It has been estimated to have a length of from 3 to 6 days (Baroyan et al., 1977; Benenson, 1981).

Transmission of the influenza virus occurs as a result of person-person contact. The virus is spread by means of droplets from the respiratory tract of infectious individuals; these droplets enter the air through coughing, sneezing, talking, and other daily behaviors. The disease is highly seasonal, with the highest incidence occurring during the winter months. This seasonality results in an oscillation of influenza outbreaks between the Northern and Southern Hemispheres, at approximately 6 month intervals (Fine, 1982).

A number of models have been developed to describe the transmission of influenza. Fine (1982) classifies these models into four types: 1) family or household

studies, 2) small community studies, 3) large population studies, and 4) prediction and control studies. A fifth type of model, evolutionary models, is explicitly concerned with the effects of evolutionary shifts in virus structure on patterns of transmission. Most existing models for influenza are concerned with household transmission or large population studies.

Household transmission studies are used primarily to aid in understanding factors that influence the likelihood that an infection is passed from one individual to another. Because of the limited size of households, it is easier to measure the degree of interaction among individuals and the chain of infection than in the population setting.

Most early models for the household transmission of infection were developed for measles and the common cold rather than for influenza, but the techniques developed are valid for influenza transmission as well. The models most often used are based on the chain binomial model, of which the Reed-Frost formulation is a special case. Chain binomial models assume as a first approximation that the latent and incubation periods are constant, that the period of infectiousness is reduced to a single point, and that there is permanent immunity following infection. If the infection in a group of susceptible individuals is started by a single infective individual or by the simultaneous introduction of several infectious cases, then the process of disease transmission will occur in a series of stages, separated from each other by a time equal to the latent period (Bailey, 1975). The process continues as long as the chain of transmission remains unbroken.

The simplest form of the chain binomial model was developed by Greenwood (1931). He assumed that each individual had a constant probability of becoming infected during each time interval. The Reed-Frost model, which is presented in detail above, assumes that the probability of infection is not constant; rather, it is a function of the number of infectious individuals in the population. These two formulations are equivalent if there is a single infectious individual who transmits the infection to only one other individual before recovering. An extensive review of chain binomial models can be found in Bailey (1975).

Early applications of the chain binomial model to the household transmission of influenza include the work of Hope Simpson and Sutherland (1954), Sugiyama (1960, 1961), and Yamamoto (1959). Hope Simpson and Sutherland studied the transmission of influenza within Gloucestershire families during the late 1940s and found no conclusive evidence for within-household transmission. Sugiyama and Yamamoto studied the transmission of Asian influenza in Osaka and considered transmission both within and outside the household. They found that the risk of intrahousehold transmission was several times greater than the risk for extrahousehold transmission.

More recent models of the household transmission of influenza have been developed and analyzed by Longini and Koopman (1982), Longini et al. (1982, 1984), and Haber et al. (1988). The traditional parameter used to measure household transmission is the secondary attack rate, the number of cases resulting from a single infective individual in a given time interval. Classical methods for calculating this parameter fail to separate true secondary household infections from community-acquired infections or from third- and fourth-generation infections (Kemper, 1981). Longini and Koopman (1982) and Longini et al. (1982) develop a maximum likelihood procedure that separates the effects of household transmission from other sources of infection in the population and thus estimates a true within-household secondary attack rate. This procedure is then applied to data on the transmission of both influenza type A and influenza type B in Seattle, Washington, and Tecumseh, Michigan. Because the method requires no critical assumptions about the timing of infections or the length of the latent, incubation, and infectious periods, it can be used with serologic data collected from sequential serosurveys. This has significant advantages over the use of data on clinical illness (the traditional data source), as serologic data allow for the identification of asymptomatic cases, which are common with influenza infection.

Longini et al. (1984) used a simulation model developed by Elveback et al. (1976) to test further the validity of the method. They found that the estimation procedure was quite robust for parameter values that were preset within appropriate limits for influenza. They also found that the procedure would be useful for detecting contagiousness of an infection as long as the potential for neighborhood transmission was low. Significant neighborhood transmission can lead to clustering of cases among households even in the absence of within-household transmission. Longini et al. (1984) further demonstrate the importance of households as mixing groups to make connections between schools and neighborhood clusters and preschool groups.

The simulation model developed by Elveback et al. (1976) and used by Longini et al. (1984) to test their model of household transmission is intended primarily to focus on the transmission of the disease at the small-community level. This model was originally developed for enteric diseases by Elveback and colleagues at the University of Minnesota and has since been extended to the transmission of several other diseases. An extensive overview of these simulations is presented in Ackerman et al. (1984). Elveback et al. (1976) explicitly consider the transmission of influenza.

The University of Minnesota simulation models consider disease transmission within highly structured small communities. The communities are separated into five age groups: preschool, grade school, high school, young adult, and older adult. In the influenza application, the grade school and high school groups are combined into a single school, which is closed on weekends. Each of the preschool children belongs to one of 30 preschool play groups numbering from two to six persons each. Neighborhood and social mixing groups are represented by 50 clusters of three to six families. Within each cluster, persons of all ages mix. There is some overlap between social clusters and neighborhood play groups, but the overlap is not complete. The general model allows for adult mixing groups, such as office staffs, but this level of structure was not included in the influenza model. The final mixing group is the total population (Elveback et al., 1976).

Mixing within a given subgroup is assumed to be random. However, mixing within the total community is nonrandom with respect to age of individuals. In the influenza application, preschoolers and their parents make twice as many contacts per day on average as school-age children and older adults.

The model also includes flexible immunization routines and variable vaccine response patterns. It is applied to the 1957 Asian and 1968 Hong Kong pandemic strains of influenza A. Attention is focused on the vaccination of school-age children, which was suggested by the age-specific attack rates in the 1957 Asian epidemics. Results of the analysis show that the interfamily and intercluster paths a school provides are important factors in the spread of the infection through the community and that vaccination of school-age children leads to the best outcome in terms of infections prevented per child vaccinated.

Virtually all work on the spread of influenza through large populations has been directly influenced by the work of Baroyan and colleagues on the spread of influenza in the Soviet Union and Bulgaria (Baroyan and Rvachev, 1967; Baroyan et al., 1969, 1971). The model developed in these papers is based on the assumption that the patterns of geographic spread are determined largely by the patterns of movement of individuals within a population. The basic structure of the model is a set of mass-action equations for the transmission of the infection within populations modified to include mobility between populations and variable duration of infectiousness. The model considers the spread within and among 100 cities and 28 nonurban regions.

Early versions of the model based the movement of individuals between cities on an empirical relationship that implied that the daily immigration rate was proportional to the sizes of the populations of each city. Later versions of the model replaced this empirical formulation with actual estimates of daily migration rates

between cities. These estimates were based on official statistics for bus, rail, and air transport between population centers included in the model.

The model also assumes that the rate of mobility from location i to location j is equal to the rate of mobility from location j to location i. Although this assumption does limit the number of parameters to be estimated because it results in a symmetric mobility matrix, it is not a particularly realistic assumption. Some cities in an area are more likely to draw a disproportionate number of travelers because of cultural, political, or economic activities, whereas other cities may have fewer visitors. However, for large-scale patterns of epidemic spread, such as those addressed by these studies, the assumption of symmetric mixing does not seem too unreasonable. Results from simulations based on the model provided both reasonable reproductions of prior epidemics and relatively successful forecasting of broad patterns of transmission throughout the study area.

Because of the success of forecasting influenza epidemics in the Soviet Union, there have been a few recent attempts to apply the Baroyan-Rvachev model to other localities. Spicer (1979) attempted to test the validity of the model on data from England and Wales. The two studies are not totally comparable, however, because there are some important differences in the types of data available from the two study areas. In the Soviet Union, there are daily notifications of acute respiratory infections, while in England and Wales the only available data are deaths per week registered as due to influenza and influenzal pneumonia. Adjustments were made to the model to deal with these data problems.

A more serious shortcoming is the lack of data on the transportation network in England and Wales. This cannot be solved by adjustments to the model, since there is no logical basis for any simplifying assumptions. Consequently, Spicer (1979) simply looked at the distribution of numbers of deaths in England and Wales and in greater London and ignored the spatial spread altogether. Although there was reasonable agreement between the predictions of the model and the actual data, the real contribution of the Baroyan-Rvachev model is in forecasting the geographic spread of the epidemic, an issue which the Spicer model was unable to address.

A better application of this model focuses on the global spread of influenza among 52 cities worldwide (Rvachev and Longini, 1985; Longini et al., 1986; Longini, 1988). Using essentially the same model as the previous work, these studies attempted to forecast the global spread of the Hong Kong pandemic of 1968–1969. Parameters were estimated from data from Hong Kong, the first city to report the appearance of the appropriate strain of influenza. The transportation network linking the 52 cities worldwide was based on air-transport data. The resulting forecast was shown to reproduce the general pattern of temporal and spatial spread of the actual epidemic as documented by World Health Organization sources.

The development of appropriate control efforts has been a major factor leading to the formulation of mathematical models for many infectious diseases. This is not the case for influenza, however. Most influenza models focus on describing the existing patterns of infection; very few have considered how best to control the disease. Exceptions to this include the preliminary studies on the importance of vaccination for influenza as reported by Elveback et al. (1976). These studies were elaborated and extended in Longini et al. (1978), who couple the deterministic model for influenza A used in Elveback et al. with an optimization formulation that determines the optimal vaccination distribution pattern among the various age groups when the quantity of vaccine is limited. These patterns are found to vary depending on the particular strain of the virus, the quantity of vaccine available, the relative costs of the control strategy, and the underlying objectives for disease control.

One final topic of interest to modelers of influenza is how to build into models the rapid evolutionary change observed in the structure of the virus. This is important because many of the serious effects of influenza at the population level result from

the fact that populations are continually exposed to new strains for which there is no previous immunity. This tends to result in periodic, serious epidemics with high rates of illness at all ages and increased mortality among the very young, very old, and other high risk groups.

Recent models developed by Pease (1987) and Andreasen (1990) address the problem of evolution of the virus. Andreasen's model presents a static picture of the influenza virus evolution that focuses on frequency-dependent selection mediated by the host population. Results from this model show that for some parameter sets more than one strain of the virus can simultaneously circulate in a population.

Pease's model allows for only one circulating strain at a time, but this strain can undergo antigenic drift with a new variant simultaneously replacing the previous one in the entire population. In this model, susceptibles are continually reintroduced into the population, not because of immigration or loss of immunity, but because of evolutionary changes in the virus that make previously immune individuals susceptible.

Analysis of Pease's model shows that the equilibrium number of infected hosts, the interepidemic period, and the probability that a host will become reinfected depend on the rate of amino acid substitution in the pathogen, the effect of these substitutions on host immunity, the host population size, and the recovery rate from the disease. Results also show that this model has no threshold population size, which implies that the disease will be endemic in populations of any size. These results suggest that there is an alternative mechanism for the maintenance of a disease in a population and that, given that influenza does evolve rapidly over time, it may be difficult or impossible to eradicate the disease.

Observations of influenza in actual populations indicate that, although several strains can be circulating in a population at one time, in most cases only one strain dominates during an epidemic (Kendal et al., 1979). It seems likely that in order to explain this observation, the approaches of Pease (1987) and Andreasen (1990) will need to be combined into a single model.

Malaria

The use of mathematical approaches in the study of malaria has one of the longest histories in all of mathematical epidemiology. There have been more than 75 years of mathematical contributions to malaria epidemiology and control since Ross first began publishing in the early 1900s (Ross, 1911). Bruce-Chwatt (1969) presents an interesting review of the early development of malaria models and the personalities involved. Because of this long history, an exhaustive review of the literature on models for the transmission of malaria is beyond the scope of this paper; there have been complete books written solely on the biomathematics of malaria (Bailey, 1982). Consequently, this section discusses the basic epidemiological principles associated with malaria modeling, a few of the models that have been developed to describe the transmission of the disease, and some of the interesting questions addressed in recent work.

Malaria in humans occurs as a consequence of infection with one of four species of the parasitic protozoan, *Plasmodium*. *P. falciparum* causes the most serious illness and is the most widespread in the tropics. For this reason, most models of malaria transmission are concerned with the dynamics of infection with this species.

The life cycle of the parasite has been summarized by Aron (1988a), Aron and May (1982), and Bailey (1975). Part of the life cycle takes place in a female mosquito of the genus *Anopheles* (the vector). The remainder occurs in a human host. Transmission to the human host occurs during the bite of an infectious female mosquito whose salivary glands have been invaded by sporozoite forms of the parasite. The sporozoites then migrate to the liver, where they replicate asexually over a period of several days (the latent period). Trophozoite forms of the parasite are liberated from the liver into the bloodstream, where they penetrate the human red blood cells. The trophozoites reproduce asexually within the red blood cells,

eventually lysing the cell and releasing merozoite forms into the bloodstream. The latter form can then invade new red cells, repeating the cycle of replication within the red cell followed by lysis. The pathological effects of malaria are a consequence of parasite replication and lysis of the red blood cells. Merozoites in the blood also give rise to sexual stages called *gametocytes*, which are transmitted to mosquitoes when they bite humans (and result in infection of uninfected mosquitoes). Fertilization of male and female gametocytes occurs in the mosquito gut, and after a short period of replication and development, sporozoites are liberated from the stomach wall of the mosquito. Some of the sporozoites migrate to the mosquito's saliva and the life cycle of the parasite begins again.

Because the malaria parasite has two obligate hosts—humans and mosquitoes—mathematical models for the transmission of the disease are often more complicated than for diseases like influenza with direct human-human transmission. The earliest models for malaria transmission were developed by Ross (1911). He formulated two models, in both of which the human population size and density of mosquitoes per human are assumed constant. One of the models considers the disease dynamics in each species explicitly, and the other model collapses relevant aspects of mosquito biology into a complex parameter so that only one equation for the dynamics within humans need be considered.

In Ross' two-equation model, the rate of infection from mosquito to human was formulated, using Nedelman's (1985) notation, as a function of the proportion of infected humans *(y)*, the density of infected mosquitoes (m_{23}), the biting rate of mosquitoes on humans *(a)*, and the proportion of bites by infectious mosquitoes on susceptible humans which result in infection *(b)*. The rate of infection from human to mosquito was formulated as a function of the density of mosquitoes per human *(m)*, the density of infected mosquitoes (m_{23}), the proportion of infected humans *(y)*, and the proportion of bites by susceptible mosquitoes on infectious humans that result in infection *(c)*. In addition, the model assumes that humans recover from the infection at a constant rate r and that mosquitoes die at a constant rate μ proportional to the total density of mosquitoes. The model also assumes that there is no vertical transmission of the parasite; i.e., all newborn humans and mosquitoes are susceptible. In addition, Ross concluded that the death rate in humans was negligible in comparison with their recovery rate and that the opposite held true for mosquitoes; i.e., the recovery rate in mosquitoes was negligible in comparison with their death rate. Taking into account the recovery and death rates and the assumptions made by Ross and considering the population dynamics only of infected mosquitoes and humans, the model can be described by the following system of ordinary differential equations:

$$\frac{dy}{dt} = bm_{23}a(1-y) - ry$$

$$\frac{dm_{23}}{dt} = c(m-m_{23})ay - \mu m_{23}$$

There are a number of assumptions that limit the utility of this formulation. Note, first of all, that in the first equation the term $(1-y)$ refers to the proportion of the population that are not infected, and the formulation implies that all of these noninfected individuals are susceptible and can contract the infection. Because there is also recovery from the infection (represented by the term ry), this further implies that there is no immunity to reinfection. The model thus falls into the *SIS* class of epidemic models. Although full immunity to malaria does not often develop, the assumption of no immunity is not totally realistic. Models that relax the assumption of no immunity will be described briefly below.

A second assumption of the model is "that an individual infected with malaria could not be again infected until after complete recovery from the initial infection"

(Ross, 1911). This is not a good assumption for malaria transmission because of the possibility of superinfection with two or more strains. Macdonald (1965) extended the Ross model with an assumption that "the existence of infection is no barrier to superinfection so that two or more broods of organisms may flourish side by side, the duration of infection due to one being unaltered by others." However, Macdonald's formulation did not properly translate his assumption. Attempts have been made to correct the formulation by Bailey (1957), Dietz et al. (1974), Nedelman (1984b), and Dietz (1988a,b) using methods developed by Kostitzin (1934). (For an English translation of Kostitzin's monograph, see Kostitzin, 1978.) McKendrick (1926) also developed an early model incorporating the possibility of superinfection.

In Ross' single equation model, the rate of new infections is a function of the rate per mosquito at which humans are bitten *(a)*, the proportion of bites by infectious mosquitoes on susceptible humans that result in infection of the human *(b)*, the proportion of bites by susceptible mosquitoes on infectious humans that result in infection of the mosquito *(c)*, the density of the biting mosquito population per human *(m)*, the death rate of mosquitoes (μ), the recovery rate in humans *(r)*, and the proportion of infected humans in the population *(y)*. Again, using the notation of Nedelman (1985), the dynamics of transmission can be represented by the following equation:

$$\frac{dy}{dt} = \left(\frac{bcma^2}{\mu}\right) y(1 - y) - ry$$

The term $(bcma^2/\mu)$ y is called the *inoculation rate* and gives the probability per unit time that an uninfected human becomes infected. This single-equation model follows from the two-equation model when it is assumed that the mosquito population equilibrates rapidly relative to the human population (Nedelman, 1985; May and Anderson, 1979).

The term $bcma^2/\mu$ in this model combines all of the mosquito dynamics into a single complex parameter. This practice of implicitly considering mosquito dynamics, although obviously incorporated into Ross' models, was defined formally as an epidemiological index by Garrett-Jones (1964). He coined the term *vectorial capacity* to describe the relevant aspects of mosquito dynamics, although he created the concept independently of any dynamic model and included the incubation period of the parasite in his original ideas. In addition, Garrett-Jones' formulation does not include the probabilities of transmission per bite of infectious mosquito. The logic used by Garrett-Jones in the development of this concept can be described as follows (after Nedelman, 1985; Bailey, 1975):

ma = the average number of mosquito bites per individual per day;
$exp(-N_2\mu)$ = the probability that a mosquito survives through its incubation period, where N_2 is the length of the incubation period (not included in the model developed by Ross);
a/μ = the average number of bites a mosquito delivers (since $1/\mu$ is the average life of a mosquito.

The vectorial capacity described by Garrett-Jones is the product of these three factors $(= ma^2exp(-N_2\mu)/\mu)$. The construction of the vectorial capacity remains unchanged when temporal variation in mosquito densities are introduced, with the exception that the index becomes a function of time because the density of mosquitoes, m, varies over time.

Although the single-equation model developed by Ross is a very simplified model, five major insights into the epidemiology of malaria have resulted from it (Molineaux, 1985). First, the model shows that there is a nonzero critical level of

the vectorial capacity, below which the disease cannot maintain itself in a population. Second, above the critical level, the relationship between vectorial capacity and prevalence of malaria is highly nonlinear. Close to the critical level, small changes in vectorial capacity lead to large changes in prevalence of the disease. At higher levels, even large changes in vectorial capacity do not change the prevalence of the disease. Third, a drastic reduction in the prevalence of malaria, without corresponding change in the vectorial capacity, does not lead to long-term changes in prevalence of the disease. Fourth, a reduction in the vectorial capacity to a lower level that remains above the critical level will lead gradually to a lower equilibrium prevalence of the disease. Fifth, the critical vectorial capacity is lower for longer lasting infections (for example, it is lower for *P. vivax* than for *P. falciparum*).

The concept of critical vectorial capacity is tied closely to the concept of basic reproductive rate discussed above. This rate, R_0, can be interpreted as the number of secondary infections that one infection could produce during the duration of the infection if both host and vector populations were uninfected. It indicates the potential for transmission deriving from a single person and suggests the potential difficulty for controlling or eradicating a disease (Aron, 1988b). If $R_0 < 1$, then a disease will die out; if $R_0 \geq 1$, the disease can persist in a population.

R_0 can be related to the vectorial capacity formulated by Garrett-Jones (1964) by the equation $R_0 = Cbc/r$, where C is the vectorial capacity, b is the proportion of bites by infectious mosquitoes on susceptible humans that result in infection, c is the proportion of bites by uninfected mosquitoes on infected humans that result in infection in the vector, and $1/r$ is the duration of one human infection. In most practical estimates of R_0, b and c are set equal to 1, resulting in extremely high values of R_0 (Dietz, 1988b).

Another very useful model for the transmission of malaria was developed by Dietz et al. (1974), Molineaux et al. (1978), and Molineaux and Gramiccia (1980) to describe the transmission of *P. falciparum* in the Garki district of northern Nigeria. This model allows for the acquisition of partial immunity to the disease, which is characterized by an increase in the recovery rate and a decrease in infectivity and detectability (Molineaux, 1985). It ignores the effects of maternal immunity, the delayed appearance of infective gametocytes, and the loss of immunity. However, the model calculates much more realistic estimates of the prevalence of the parasite, including variation by age, season, place, and differential control, than do other models. In spite of this greater success at modeling the distribution of the disease, the model has been used more as a teaching tool than for planning control strategies or guiding research. Even with the advances in mathematical epidemiology that have been made in the last 75 years, the complexities of malaria transmission in a natural environment still limit the direct practical usefulness of models of transmission.

In addition to these general models for the transmission of malaria, a few models that look at other specific aspects of the natural history of the disease have been developed. The basic models assume constant contact rates of vector per human and human per vector. These are not realistic assumptions. There is some evidence for variability of the biting rates of mosquitoes with age of the human (Muirhead-Thomson, 1951; Carnevale et al., 1978; Shidrawi et al., 1974; Nedelman, 1984a). In several studies, this kind of variability has been shown to increase the basic reproductive rate (Dietz, 1980; Dye and Hasibeder, 1986; Hasibeder and Dye, 1988).

The second assumption, that the rate of contact with infectious humans is random, is also not realistic. Several studies have suggested that mosquitoes do not feed randomly with respect to host infection. Nonrandom feeding may occur at three different stages: attraction and penetration, probing and the location of blood, and blood intake (Edman et al., 1985). Studies that have demonstrated probable nonrandom feeding of mosquitoes on hosts infected with various diseases have been reviewed by Kingsolver (1987). These studies suggest that blood-sucking mosquitoes may preferentially choose hosts infected with malaria para-

sites. Kingsolver also develops and analyzes a simple model for the dynamics of malarial transmission that incorporates such nonrandom feeding behavior by the mosquito. Results of the analysis of this model indicate that preference for infected hosts makes it easier to maintain the infection at an endemic level.

Another problem with the basic malaria models is that they do not take into account any aspects of host immunity. Dietz et al. (1974) first considered this problem in the development of their model for the Garki project. More recent models that focus on the development of immunity to malaria include Dutertre (1976), Elderkin et al. (1977), Aron and May (1982), and Aron (1983, 1988a). The inclusion of immunity into malaria is most important if the populations being modeled have prevalences far above the critical level of the basic reproductive rate, a situation that is the norm in natural populations.

A final focus for mathematical models of malaria transmission is the possible effectiveness of a vaccine for malaria. Struchiner et al. (1989) and Halloran et al. (1989) have modified the Garki model for this purpose. Simulations based on their model reproduce observed periodic fluctuations of malaria prevalence in areas of unstable transmission. The simulations are used to evaluate the consequences of different types of immunization programs on the prevalence of infection and disease. Fluctuations of malaria prevalence observed in the simulations (and in the real world) are attributed to the interplay of transmission-blocking immunity and a loss of immunity in the absence of boosting through infection or vaccination. However, in regions with periodic malaria, there is also periodic rainfall, and there is evidence that cycles of rainfall may have a major role in driving the epidemic cycles (Aron, personal communication).

The use of mathematical models to describe the transmission of malaria has been closely tied to practical aspects involved with the control of the disease since the very first attempt at formulating a model. Significant increases in the understanding of the biological factors affecting transmission of the disease have resulted from these studies, but there is obviously much work left to be done before we will understand fully the factors involved in determining prevalence levels of the disease and the most appropriate ways to attempt to control the spread of the disease.

AIDS

Although AIDS has been recognized as a distinct entity for less than a decade (or perhaps *because* it has such a short history), the number and sophistication of models for the transmission of the disease probably equal or exceed that for any disease other than malaria. In 1989 alone, three volumes with significant contributions to mathematical epidemiology were published: *Applied Mathematical Ecology,* edited by S.A. Levin, T.G. Hallam, and L.J. Gross, which has eight papers on mathematical epidemiology, two of which are devoted to AIDS models; *Mathematical Approaches to Problems in Resource Management and Epidemiology,* edited by C. Castillo-Chavez, S.A. Levin, and C.A. Shoemaker, which has five general models and four papers with AIDS models; and *Mathematical and Statistical Approaches to AIDS Epidemiology,* edited by C. Castillo-Chavez, which has 19 papers, all devoted to modeling the HIV transmission system.

Because of the large number of models that have been developed and the variety of questions they are directed toward answering, it is helpful to summarize briefly the relevant features of the epidemiology of AIDS. AIDS is a clinical syndrome associated with severe damage to the immune system as a consequence of infection with a retrovirus, human immunodeficiency virus (HIV). Because of the immune suppression, a number of opportunistic infections, rare cancers, and other unusual infections may occur. These are the immediate causes of death among AIDS patients. The earliest marker to indicate infection is usually seroconversion, where antibodies to HIV begin to be detected in the serum of the individual. The average time to seroconversion is estimated to be about 2–6 months. At some point after infection, more than 90% of individuals will start to show an initial immune

suppression. AIDS itself develops in most, if not all, infected individuals who do not die from other causes.

There are three primary modes of transmission of the virus: 1) sexual activity, 2) blood and blood products, and 3) perinatal transmission. As a consequence of these modes of transmission, the biology of the virus, and the history of the virus in human populations, there are seven recognized high-risk groups: 1) homosexual or bisexual males; 2) intravenous drug users; 3) sexual contacts of intravenous drug users (both male and female); 4) recipients of blood transfusions (prior to 1985 in the United States and Western Europe); 5) hemophiliacs; 6) sexual contacts of transfusion recipients and hemophiliacs; and 7) children of infected individuals.

The proportions of reported cases in different risk groups remained relatively constant during the mid-1980s, with about 65% of all cases in the United States occurring among homosexual males, another 20% occurring among intravenous drug users (both heterosexual and homosexual), and the remaining 15% from other risk groups or with unknown risk factors (Centers for Disease Control, 1987). Recently there has been a decrease in the proportion of males whose only apparent risk factor was homosexual activity (from 70% of cases reported in 1987 to 63% in 1988) and an increase in the proportion of cases among intravenous drug users. This change is likely due to a combination of the effects of the 1987 revision of the case definition for AIDS and changing incidence rates in the homosexual and intravenous drug using populations (Centers for Disease Control, 1989). The proportions of reported cases outside of the United States are very different, with much less evidence for a bias toward males because of greater relative frequency of heterosexual transmission as opposed to homosexual transmission.

Realistic models for the spread of HIV should consider all of the risk groups mentioned, but because of a lack of detailed information on the type and frequency of human interactions that link risk groups, most existing models are limited to only one or two groups. In addition to the risk groups themselves, there are a number of other factors commonly considered in models of HIV transmission. These include the frequency of sexual behavior (which has been estimated to range from 0 to more than 50 partners per year for homosexual males (data from BMRB, 1987, cited in May and Anderson, 1988), the nature of the sexual behaviors and preventive measures taken, geographic location, age distribution of the population (since sexual behavior and intravenous drug use are clearly age dependent), behaviors associated with IV drug use, such as sharing needles or using rented equipment, and the patterns of interaction among individuals within and between risk groups. Models for HIV transmission also generally include two main factors associated with the natural history of the disease: 1) the pattern of infectivity, which probably is not constant throughout the infectious period; and 2) the progression of the disease within an individual. This last factor is important because the individual behaviors and possibly the infectivity of the virus are likely to vary in different stages of the disease.

Because there are such well-defined risk groups for HIV transmission and because there clearly is nonrandom mixing among risk groups, reasonable models for HIV transmission must consider structured populations. Rather than having one large, randomly mixing population, these models assume that the population is divided into a number of subpopulations within which mixing is usually assumed to be random but among which mixing is nonrandom.

Most existing models for the transmission of HIV consider only the sexual transmission of the disease, largely because, as a consequence of historical factors, there are better data available for this problem. A few recent papers, however, address the transmission of the disease within intravenous drug-using populations (for example, Kaplan, 1989c; Blower and Medley, 1990).

As with models for most other diseases, there are both statistical and mathematical approaches in models of AIDS transmission. The statistical approaches are generally concerned either with short-term forecasting of the epidemic or with the estimation of the relevant parameters in dynamic AIDS models. A recent review of

the major questions, methods, and problems associated with these approaches can be found in Schwager et al. (1989). Recent papers concerned with short-term forecasting or estimation of parameters include Boldsen et al. (1988), DeGruttola and Lagakos (1989), Healy and Tillett (1988), Karon et al. (1989), Layne et al. (1989), and Longini et al. (1989).

Mathematical models focus more on the natural history of the virus and the relevant social dynamics affecting the transmission of the virus through a population. Most early models and a few more recent models of the transmission of HIV incorporated aspects of the natural history of the virus into the model, but these were concerned primarily with projecting the spread and impact of the disease given the limited data available. Pickering et al. (1986) developed a model in which the probability of transmission depended on the length of the incubation period, variable infectivity, level of infection within a population, and changes in sexual behavior. Knox (1986) considered variations in the removal rate, the new partner acquisition rate, and the infectivity on equilibrium levels for prevalence and incidence. DeGruttola and Mayer (1988) developed a model for heterosexual spread of HIV and fit the results to surveillance data on prevalence of the infection. Wilkie (1988) developed an actuarial model for AIDS that could be used to aid in the development of insurance policies. Such a goal requires the best possible estimates of long-term trends of the disease. Aron and Sarma (1989) analyze demographically data on sexual behavior in the United States to project the potential impact of AIDS on the heterosexual population. Hethcote (1989) developed a model for the transmission of HIV that incorporates homosexual transmission, heterosexual transmission, and intravenous drug use. His model was intended to aid in an assessment of the effects of all the major modes of transmission on the spread of the virus through a population. Bailey (1988) advocated the development of relatively simplified models that could be used by decision makers to act more effectively immediately. Mode et al. (1988) developed a stochastic computer model of an AIDS epidemic to explore the consequences of ignoring random effects in transmission on projections of the epidemic. Results of the analysis of their model showed that predictions from deterministic models may be overly pessimistic.

One consequence of the analysis of many of these projection models was a recognition of the sensitivity of predictions to the parameter values chosen. A variety of outcomes are possible, depending on particular choices of critical parameters. In order to have confidence in the results of model projections, it is necessary to explore the effects of variation in parameters on the spread of the disease. Because of this, many recent models are concerned more with these issues than with projections of the epidemic.

There are several specific aspects of the natural history of the disease and the behavior of the host population that models can address: 1) the effect that variability in infectivity throughout the course of the disease in an individual has on the spread of the infection through the population; 2) the role of long incubation periods in the dynamics of the disease; 3) the effect of level of sexual activity on an individual's risk for disease; 4) the effect of assumptions about mixing between groups on both individual risk and transmission throughout a population; 5) the consequences of changes in sexual behavior; and 6) the demographic consequences of the epidemic, particularly in those parts of the world, such as Africa and parts of the Caribbean, with very high rates of infection.

Blythe and Anderson (1988b), Castillo-Chavez et al. (1989c), Hyman and Stanley (1988, 1989), and Jacquez et al. (1988) have studied the effects of variation in the shape of the infectivity curve over the course of infection. These models use an infectivity curve that has a sharp peak early in the infectious period, followed by a low level of infectivity that rises gradually with the time since infection. Blythe and Anderson (1988b) and Hyman and Stanley (1988, 1989) use a continuous distribution of infectivity in their simulations, whereas simulations presented in Jacquez et al. (1988) or Castillo-Chavez et al. (1989c) are more restrictive. Results from these studies show that in a model in which all individuals have the same risk

behavior, the rate at which the susceptible population is infected changes dramatically when the infectivity curve is altered. These effects are most marked when the alterations change the early peak in infectivity. Cardell and Kanouse (1989) look at the effects of heterogeneity in both susceptibility and infectivity. Kaplan (1990) addresses potential problems inherent in existing methods for modeling HIV infectivity.

Theoretical analyses of HIV models with variable infectivity have been conducted by Thieme and Castillo-Chavez (1989; unpublished manuscript), who explore interactions between a general infectivity curve that is dependent on the time since infection, variable incubation period, and nonlinear mean sexual activity; they show that variable infectivity may lead to oscillations in disease incidence over time. This oscillatory behavior is not observed in compartmental models like those of Jacquez et al. (1988) or Castillo-Chavez et al. (1989c) that use only differential equations with constant parameters.

Models have also been developed to explore the effects of variability in the length of the incubation period (Blythe and Anderson, 1988b; Castillo-Chavez, 1989a; Castillo-Chavez et al., 1989a,b). Analyses of these models show that long incubation periods do not lead to periodic outbreaks of the disease, but in models with multiple groups there may be more than one equilibrium prevalence of disease. However, the results of Thieme and Castillo-Chavez (1989; unpublished manuscript) suggest that the interplay between variable and long incubation periods and variable mean partnership change rates can potentially change the qualitative outcome of the epidemic.

Early studies of the effect of level of sexual activity on HIV transmission include Anderson et al. (1986), Blythe and Anderson (1988a), Kießling et al. (1986), and May and Anderson (1987). These studies clearly show that the level and type of sexual activity is a critical factor influencing the rate of spread and intensity of the epidemic in each subgroup. However, these models assume proportionate mixing of individuals within the population, assumptions that previous studies on gonorrhea (for example, Hethcote and Yorke, 1984) and hepatitis A (Sattenspiel, 1987; Sattenspiel and Simon, 1988) demonstrated to be unrealistic.

The assumption of proportionate mixing was first introduced by Barbour (1978). In this type of generalized random mixing, the probability of contact between individuals from different groups is proportional to the size or amount of activity of the groups involved (Hethcote and Yorke, 1984). This is not a very realistic assumption, especially for sexually transmitted diseases, although the use of proportionate mixing in age-structured models has generated some useful practical and theoretical results (see, for example, Castillo-Chavez et al., 1988, 1989e; Dietz, 1975; Hethcote and Van Ark, 1987; Hoppensteadt, 1974; May, 1986; Schenzle, 1985; Webb, 1985).

Many recent models HIV transmission models have focused on ways to formulate social mixing more realistically (Anderson et al., 1989, 1990; Blythe and Castillo-Chavez, 1989; Busenberg and Castillo-Chavez, 1989, 1990; Castillo-Chavez and Blythe, 1989; Castillo-Chavez et al., 1990; Gupta et al., 1989; Hyman and Stanley, 1988, 1989; Jacquez et al., 1988; Koopman et al., 1988; Sattenspiel et al., 1990). Although general forms of mixing between groups have been used extensively in the population genetics literature for some time, Nold (1980) and Hethcote and Yorke (1984) were the first to address the consequences of the proportionate mixing assumption in epidemic models. They sketched ways to relax this assumption by assuming that there was a certain amount of bias for within-group mixing. These ideas were formalized and named *preferred mixing* by the Michigan HIV modeling group (Jacquez et al., 1988; Koopman et al., 1988; Sattenspiel et al., 1990). In preferred mixing, a specified proportion of contacts are made between individuals within the same group, whereas the remaining contacts occur between individuals from different groups and are made in proportion to the amount of sexual activity of the groups. Preferred mixing is thus a combination of restricted, endogamous mating and random, exogamous mating.

Generalizations to like-with-like (or assortative) mixing have been carried out by Anderson et al. (1989, 1990), Blythe and Castillo-Chavez (1989), Castillo-Chavez and Blythe (1989), Gupta et al. (1989), and Hyman and Stanley (1988, 1989). Recently, an axiomatic framework has been developed by Busenberg and Castillo-Chavez (1990; based on the work of Blythe and Castillo-Chavez, 1990) to describe one- and two-sex mixing interactions of age- and risk-structured populations. Further, formulas describing all solutions to these frameworks (i.e., formulas describing all forms of mixing) have been computed, and a simple recipe for superimposing mixing structures (such as in the case of preferred mixing) has been provided (Sattenspiel and Castillo-Chavez, 1990; Busenberg and Castillo-Chavez, 1989, 1990; and Castillo-Chavez et al., 1990).

Results from analyses of the Michigan model and other similar models show that 1) the pattern of infectivity in an individual can markedly influence the outcome of the epidemic; 2) the level of sexual activity is an important individual risk factor; and 3) the pattern of mixing among individuals profoundly affects the rate and amount of spread of the infection through the population (Castillo-Chavez et al., 1989b; Hyman and Stanley 1988, 1989; Jacquez et al., 1988; Koopman et al., 1988; Sattenspiel et al. 1990).

Recent extensions of the Michigan model generalize and restructure the mixing formulation (Jacquez et al., 1989; Koopman et al., 1989). These models divide the population into both structural and mixing groups that overlap but that are not equivalent. The mixing matrix, f, has elements f_{ij} that give the fraction of structural group i's contacts allocated to mixing group j. A mixing group may contain contributions from any number of structural groups, and a structural group may appear in any number of mixing groups. Jacquez et al. (1989) consider the nonrandom mixing associated with the definition of mixing groups; Koopman et al. (1989) explore nonrandomness associated with selection of partners within mixing groups. Kaplan et al. (1989) also explore the effects of nonrandomness in individual partner selection, and they tie choice of sexual partner to the perceived risk of infection from that partner.

The Michigan model is a special case of models developed by Blythe and Castillo-Chavez (1989), Castillo-Chavez and Blythe (1989), Castillo-Chavez et al. (1989b,d,e,), Hyman and Stanley (1988, 1989), and May et al. (1988, 1989). These more general models have continuously distributed characteristics, incorporate arbitrary incubation period distributions, and explore the effects of several factors on the shape of the mixing function, including the mean sexual activity of the population under consideration, the shape of the preference function, and the distribution of sexual activity in the population. In addition, the extensions of May et al. (1988, 1989) incorporate age structure, and the recent extensions of Busenberg and Castillo-Chavez (1989, 1990) include age and risk structure and arbitrary mixing structures.

All of the models that incorporate generalizations of proportionate mixing show that patterns of mixing can affect significantly the quantitative and qualitative outcome of the AIDS epidemic. Kaplan (1989a,b, 1991) and Kaplan and Lee (1990) address the issue of whether decisions about the management of the epidemic must necessarily depend upon complex structured models. Results from these studies show that random or proportionate mixing models usually result in "worst case scenarios" and may lead to reasonable policy decisions, even though they do not incorporate realistic sexual mixing patterns. Wiley and Herschkorn (1989), however, find that this is not always true; for fixed epidemiological conditions, a certain level of like-with-like preference may yield the "worst case scenario."

Morris (1989) has extended a basic HIV transmission model to incorporate the effects of selective mixing in both stable and nonstable populations. She found that in nonstable populations behavioral responses to changes in relative group sizes must be explicitly modeled. This is done by making the elements of the contact matrix a function of mixing preferences, which may be stable over time, and the population structure, which changes over time. In addition to these structural

considerations, log-linear models were proposed as a method to estimate statistically the underlying parameters that regulate selective mixing. Simulations based on behavioral, sociological, demographic, and epidemiological data from a number of sources were used to demonstrate the usefulness of this approach.

One question not addressed in the models described above is the effect of the social context of sexual interactions on the likelihood of transmission of the infection. These models assume that the only factors influencing transmission are characteristics associated with the assigned groups i and j of the individuals involved in an interaction. However, this is probably not a reasonable assumption. Behaviors are dynamic and plastic and tend to change when the environmental conditions change. Thus, although an individual may normally engage in certain types of sexual activities, the actual behaviors present under the conditions of a specific sexual interaction may be of higher or lower risk than normal for that individual. The risks for transmission of a disease depend on the behaviors that are occurring at the time of contact, not on the behaviors that normally occur; therefore, it is important to have some mechanism for behavioral plasticity in the model.

One way to approach modeling the effects of social context and the resulting behavioral plasticity on the spread of HIV is to define the groups on the basis of a set of risk behaviors rather than using a simple variable like number of new sexual contacts. Individuals are classified into a particular group on the basis of their usual activities, but at the time of a sexual contact they may take on behaviors characteristic of other risk groups. Because the probability of transmission will be most closely related to behaviors occurring at the time of contact, a mechanism is required to model the probability that an individual from group i takes on behaviors characteristic of a different group when that individual enters a sexual encounter. This temporary behavioral change can be described by a "movement" matrix, b, the elements of which give the probability that an individual whose normal behaviors are characteristic of risk level i engages in sexual activities characteristic of risk level j. A model incorporating this behavioral "mobility" has been developed by Sattenspiel and Castillo-Chavez (1990). Results from preliminary analyses of this model indicate that the major effects of incorporating social context include a decrease in the number of cases of the disease, sometimes by an order of magnitude or more, delayed spread of the disease, and a decreased impact of the disease on low and medium risk groups, but that the qualitative behavior of the epidemic does not change.

Castillo-Chavez (1989b) indicates that the movement matrix approach can be combined with any classical modeling approach. He and Busenberg addressed the possibility of developing such models, but because of the improbability of collecting reasonable data to validate their models, the models were not fully developed (Busenberg and Castillo-Chavez, 1989).

In addition to the temporary changes in behavior considered in this model, there is a definite need to incorporate more long-term behavioral changes in AIDS transmission models. The kinds of behavioral changes that have been or might need to be incorporated into models for AIDS are discussed by Aron and Wileyto (unpublished manuscript). Hethcote et al. (unpublished manuscript) developed a model for homosexual transmission of the virus and attempted to determine the model structure necessary to reproduce the San Francisco AIDS epidemic. They found that in order to get satisfactory fits to the data changes in sexual behavior must be included. Anderson et al. (1989) have also looked at the effects of changes in sexual behavior on the dynamics of HIV transmission in the male homosexual population in the United Kingdom. Numerical simulations show that the manner in which behavioral changes occur and who in the population is influenced by such changes have a major impact on the future time course of the epidemic. The strongest effects will occur when the behavioral changes occur disproportionately among the most active individuals in the population.

Marriage models that follow pairs of individuals and consider the dynamics of pairs have been developed by Kendall (1949) and Fredrickson (1971) to aid in

demographic projections of populations. Similar types of models for transmission of sexually transmitted diseases have been developed by Dietz (1988c), Dietz and Hadeler (1988), Waldstätter (1989), and Castillo-Chavez et al. (1990). Rather than looking at the formation of sexual partnerships at the population level, these models consider how individuals form partnerships, which allows them to address explicitly the effect of variations in the duration of partnerships as well as variability in the number of contacts with the same partner. This kind of model allows one to incorporate the effects of changing sexual activity rates with length of partnership or the consequences of infection of one partner after a variable amount of time within a partnership. These factors cannot be explored effectively with most other existing models.

There have been a few attempts to combine both the pair-formation approach and the population-level approach (Busenberg and Castillo-Chavez, 1989, 1990; Stanley, unpublished manuscript). In addition, Blythe and Castillo-Chavez (1990) have begun to explore the processes of pair formation and dissolution in the context of stochastically interacting populations.

May et al. (1988, 1989) and Anderson et al. (1988) have developed a series of models to look at the demographic consequences of the AIDS epidemic. They take a simple epidemic model and combine it with standard demographic models to explore the effects of horizontally and vertically transmitted HIV on overall growth rates and age profiles of a population. Because their models are focused on understanding basic ways that AIDS deaths might affect demographic patterns rather than predictions of prevalence and incidence rates, they simplify the epidemiology by assuming constant infectiousness, constant transmission rates, and random mixing of individuals within the population.

Finally, a number of other reviews of AIDS transmission models have been recently published (Anderson, 1988, 1989; Isham, 1988; May and Anderson, 1988; Schwager et al., 1989). These emphasize different aspects of the development and analysis of AIDS models than those presented here.

FUTURE DIRECTIONS

The volume and sophistication of papers in mathematical epidemiology is truly impressive. Many important insights into the nature of disease spread and the factors that are important in attempting to control it have been made in the last few decades. However, in spite of great increases in understanding of the mechanism of disease spread, mathematical models are still limited in their ability to aid significantly in the determination of appropriate control policies. One reason for this is that many models are better suited to advancing theoretical understanding than to economic policy making.

In addition, there is one weakness of many of these models that may also help to explain a general disappointment in the ability of mathematical models to affect the development of control policies. This weakness is that there is too little attention paid to human cultural and behavioral factors in the formulation of the models. This is not true for all models. In particular, the AIDS models that are being developed, some of the household and geographic studies for influenza, and the measles work of Cliff and his colleagues (Cliff and Haggett 1980, 1984; Cliff et al. 1975, 1981; Cliff and Murray 1977; Haggett 1972, 1976, 1982) pay close attention to ways in which human behavior affects disease spread. However, the majority of mathematical models are still being developed by ecologists, parasitologists, and mathematicians, who have a tendency to focus on the biology of the infectious organism and possibly a vector species, but who tend to take human biology and behavior as a constant.

This is most clearly seen in the malaria models discussed above and in models for other parasitic diseases. Anthropologists have made major contributions to understanding the cultural factors involved in genetic changes associated with malaria; but where are the human factors in epidemiological models? There is extensive attention to mosquito dynamics, but the models do not consider aspects of human behavior, such as agricultural practices, preventive measures taken by native

populations, or other behaviors that affect the likelihood of mosquito-human contact. There is abundant opportunity for anthropologists, who usually begin learning about malaria in their very first anthropology course, to combine the sort of work that has been done in anthropological genetics with models that have been developed already for malaria control. Wiesenfeld (1967) did make an early attempt at combining population genetic models with early epidemiological models for malaria dynamics, but so many advances have been made in both population genetics and mathematical epidemiology that new studies similar to his are certainly justified.

Because of the public health emergency associated with AIDS, because of the historical timing of the disease, and because of the type of transmission of the disease, most AIDS models focus extensively on human behavioral factors. This has been aided by the active involvement of a few anthropologists, sociologists, and other social scientists in close collaboration with epidemiologists and biologists. There is still much to be done. Very sophisticated models have been developed, but by and large they are concerned with the problem in the developed world. The effects of the disease will be much more severe in parts of the developing world, such as Africa and the Caribbean. What mathematical epidemiologists need are collaborations with mathematically sophisticated anthropologists who specialize in these parts of the world so that models that incorporate cultural behaviors specific to these areas can be developed. There are already indications that differences in epidemic patterns between developed and developing countries are largely the consequence of cultural differences in behavior rather than differences in biology.

Finally, this review considered models that have been developed to help understand the spread of influenza. Reasonable attempts have been made at incorporating some aspects of human behavior in models for global transmission. However, additional studies focusing on human interactions on a day-to-day basis are needed. This is especially important in studies of household transmission, as the likelihood of transmission is strongly influenced by personal interactions on a very small scale. The household transmission models implicitly consider human interactions, but they assume that all individuals within a household are engaging in the same types of interactions at the same frequency. This is clearly not realistic; there is significant social structuring at even the household level. This differential interaction is probably a major factor affecting whether or not an individual escapes infection, even though one or more household members are infected.

The small community studies of Elveback and colleagues at the University of Minnesota (Elveback et al., 1976; Ackerman et al., 1984; Longini et al., 1978) have been more effective in describing disease spread through a community than many other approaches, largely because of their attention to the day-to-day behaviors of individuals. They do build in different levels of interaction among individuals: young adults (parents) and preschool-age children have more frequent social interactions than school-age children and older adults. The development of larger and faster computers will guarantee that this kind of approach can be used more generally.

The field of mathematical epidemiology has come a long way in the last few decades. However, there is a crucial need to incorporate more human elements into the modeling efforts. Without significantly more attention to the ways human behaviors influence transmission, mathematical models will continue to enhance our theoretical understanding of the biological mechanisms of disease spread but will do little to aid in attempts to control the spread of infectious diseases.

In addition, the techniques and models of mathematical epidemiology may be of some use in providing some measure of scientific rigor to our speculative ideas about disease in prehistory. Over the last few decades, abundant demographic data have been collected in small anthropological populations. Insights from the analysis of these data can be combined with archaeological data to develop possible models for the demographic structure of prehistoric populations at particular places and times. Particular diseases can then be introduced into these popula-

tions, and epidemics can be simulated using models similar to those described above.

Given that early human populations were almost certainly composed of very small, semi-isolated groups, a simple Reed-Frost or mass-action model (as found in McGrath, 1988; Milner 1980; Ramenofsky, 1987; or Upham, 1986) is not likely to be sufficient to describe the patterns of disease spread and the consequent impact of infectious diseases on mortality and morbidity patterns in such populations. At the very least, one would need to incorporate population subdivision and nonrandom mixing within and among groups into the models. In addition, knowledge of the biological dynamics of likely diseases must be incorporated into the models. However, knowledge available from living populations on culture, demography, and biological properties of disease organisms should allow reasonable models to be built to describe the impact of infectious diseases on pre-Colonial Native American populations, on populations undergoing the transition from hunting and gathering to incipient agriculture, on early urban populations, and on other groups of interest to anthropologists.

Biological anthropologists are eminently suited to combining the necessary types of biological knowledge with knowledge of the population structure and cultural factors in the development of models to describe disease transmission in both modern and prehistoric populations. Given that disease is both a cultural and a biological entity, the inclusion of both cultural and biological factors in disease modeling should be a key factor allowing the development of truly useful models.

ACKNOWLEDGMENTS

I thank all of the authors who generously and promptly sent me copies of their relevant articles. Special thanks also go to Joan Aron and Lynn Jorde for their helpful comments and to Christopher Powell, who helped sift through hundreds of potential references.

LITERATURE CITED

Abbey H (1952) An examination of the Reed-Frost theory of epidemics. Hum. Biol. *24:*201–233.

Ackerman E, Elveback LR, and Fox JP (1984) Simulation of Infectious Disease Epidemics. Springfield, Illinois: C.C. Thomas.

Anderson RM (1988) The role of mathematical models in the study of HIV transmission and the epidemiology of AIDS. J. Aids *1:*241–256.

Anderson RM (1989) Mathematical and statistical studies of the epidemiology of HIV. AIDS *3:*333–346.

Anderson RM and May RM (1985) Age-related changes in the rate of disease transmission: implications to the design of vaccination programmes. J. Hyg. *94:*365–436.

Anderson RM, Blythe SP, Gupta S, and Konings E (1989) The transmission dynamics of the human immunodeficiency virus type 1 in the male homosexual community in the United Kingdom: The influence of changes in sexual behavior. Philos. Trans. R. Soc. Lond. [Biol] *325:*45–98.

Anderson RM, Gupta S, and Ng W (1990) The significance of sexual partner contact networks for the transmission dynamics of HIV. J. AIDS (in press).

Anderson RM, May RM, and McLean AR (1988) Possible demographic consequences of AIDS in developing countries. Nature *332:*228–234.

Anderson RM, Medley GF, May RM, and Johnson AM (1986) A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. IMA J. Math. Med. Biol. *3:*229–263.

Andreasen V (1990) SIR models of the epidemiology and natural selection of co-circulating influenza virus with partial cross-immunity. Tekst Nr. 192, IMFUFA, Roskilde Universitetscenter, Denmark, pp. 17–37.

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

Angulo JJ (1987) Interdisciplinary approaches in epidemic studies—II. Four geographic models of the flow of contagious disease. Soc. Sci. Med. *24:* 57–69.

Angulo JJ, Pederneiras CAA, Ebner W, Kimura EM, and Megale P (1980) Concepts of diffusion theory and a graphic approach to the description of the epidemic flow of contagious disease. Public Health Rep. *95:*478–485.

Angulo JJ, Takaguti CK, Pederneiras CAA, Carvalho-de-Souza AM, Oliveira-de-Souza MC, and Megale P (1979) Identification of pattern and process in the spread of contagious disease. Soc. Sci. Med. *13D:*183–189.

Armelagos GJ and Dewey JR (1970) Evolutionary response to human infectious diseases. Biosciences *20:*271–275.

Aron JL (1983) Dynamics of acquired immunity boosted by exposure to infection. Math. Biosci. *64:*249–259.

Aron JL (1988a) Mathematical modeling of immunity to malaria. Math. Biosci. *90:*385–396.

Aron JL (1988b) Disease control and mortality reduction. Res. Hum. Capital Dev. *5:*43–56.

Aron JL and May RM (1982) The population dy-

namics of malaria. In RM Anderson (ed.): Population Dynamics of Infectious Diseases. London: Chapman and Hall, pp. 139–179.
Aron JL and Sarma PS (1989) Assessment of the risk of HIV spread via non-steady heterosexual partners in the U.S. population. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 178–199.
Bailey NTJ (1957) The Mathematical Theory of Epidemics. London: Charles Griffin.
Bailey NTJ (1975) The Mathematical Theory of Infectious Diseases and its Applications. New York: Hafner Press.
Bailey NTJ (1982) The Biomathematics of Malaria. London: Charles Griffin.
Bailey NTJ (1988) Simplified modelling of the population dynamics of HIV/AIDS. J. R. Statist. Soc. A *151:*31–34.
Barbour AD (1978) Macdonald's model and the transmission of bilharzia. Trans. R. Soc. Trop. Med. Hyg. *72:*6–15.
Baroyan OV, Genchikov LA, Rvachev LA, and Shashkov VA (1969) An attempt at large-scale influenza epidemic modelling by means of a computer. Bull. Int. Epidemiol. Assoc. *18:*22–31.
Baroyan OV and Rvachev LA (1967) Deterministic models of epidemics for a territory with a transport network. Cybernetics (Kibernetika) *3:* 67–74.
Baroyan OV, Rvachev LA, Basilevsky UV, Ermakov VV, Frank KD, Rvachev MA, and Shashkov VA (1971) Computer modelling of influenza epidemics for the whole country (USSR). Adv. Appl. Prob. *3:*224–226.
Baroyan OV, Rvachev LA, and Ivannikov YG (1977) Modeling and Forecasting of Influenza Epidemics for the Territory of the USSR. Moscow: Gameleya Institute of Epidemiology and Microbiology. (in Russian)
Bartlett MS (1960) The critical community size for measles in the United States. J. R. Statist. Soc. A *123:*37–44.
Becker N (1981) The infectiousness of a disease within households. Biometrika *68:*133–141.
Benenson AS (ed.) (1981) Control of Communicable Diseases in Man, 13th ed. Washington, D.C.: The American Public Health Association.
Black FL (1966) Measles endemicity in insular populations: critical community size and its evolutionary implication. J. Theor. Biol. *11:*207–211.
Black FL (1975) Infectious diseases in primitive societies. Science *187:*515–518.
Blower SM and Medley GF (1990) Epidemiology, HIV & drugs: Mathematical models & data. Br. J. Addict. (in press)
Blythe SP and Anderson RM (1988a) Heterogeneous sexual activity models of HIV transmission in male homosexual populations. IMA J. Math. Appl. Med. Biol. *5:*237–260.
Blythe SP and Anderson RM (1988b) Variable infectiousness in HIV transmission models. IMA J. Math. Appl. Med. Biol. *5:*181–200.
Blythe SP and Castillo-Chavez C (1989) Like-with-like preference and sexual mixing models. Math. Biosci. *96:*221–238.
Blythe SP and Castillo-Chavez C (1990) Scaling of sexual activity. Nature *344:*202.
BMRB (1987) AIDS Advertising Campaign: Report for Surveys During the First Year of Advertising. London: British Market Research Board.
Boldsen JL, Jensen JL, Søgaard J, and Sørensen M (1988) On the incubation time distribution and the Danish AIDS data. J. R. Statist. Soc. A *151:* 42–43.
Bongaarts J (1989) A model of the spread of HIV infection and the demographic impact of AIDS. Statis. Med. *8:*103–120.
Brøgger S (1967) Systems analysis in tuberculosis control: A model. Annu. Rev. Respir. Dis. *95:* 419–434.
Bruce-Chwatt LJ (1969) George Macdonald Memorial Lecture: Quantitative epidemiology of tropical diseases. Trans. R. Soc. Trop. Med. Hyg. *63:*131–143.
Busenberg S and Castillo-Chavez C (1989) Interaction, pair formation and force of infection terms in sexually transmitted diseases. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 289–300.
Busenberg S and Castillo-Chavez C (1990) On the role of preference in the solution of the mixing problem, and its application to risk- and age-structured epidemic models. IMA J. Math. Appl. Med. Biol. (in press).
Cardell NS and Kanouse DE (1989) Modeling heterogeneity in susceptibility and infectivity for HIV infection. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 138–156.
Carnevale P, Frézil JL, Bosseno MF, Le Pont F, and Lancien J (1978) Etude de l'aggressivité d'Anopheles gambiae A en fonction de l'age et du sexe des sujets humains. Bull. WHO *56:*147–156.
Castillo-Chavez C (1989a) Recent models of HIV/AIDS transmission. In SA Levin, TG Hallam, and LJ Gross (eds.) Applied Mathematical Ecology, Biomathematics 18. Berlin: Springer-Verlag, pp. 253–262.
Castillo-Chavez C (1989b) Structured models: some modeling applications. In SA Levin, TG Hallam, and LJ Gross (eds.): Applied Mathematical Ecology, Biomathematics 18. Berlin: Springer-Verlag, pp. 450–470.
Castillo-Chavez C (ed.) (1989c) Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag.
Castillo-Chavez C and Blythe SP (1989) Mixing framework for social/sexual behavior. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 275–288.
Castillo-Chavez C, Busenberg S, and Gerow K (1990) Pair formation in structured populations. In Goldstein, Koppel, and Schappacher (eds.): Differential Equations with Applications in Biology, Physics, and Engineering. New York: Dekker. (in press).
Castillo-Chavez C, Cooke KL, Huang W, and Levin SA (1989a) On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (AIDS). Part I: Single population models. J. Math. Biol. *27:*373–398.
Castillo-Chavez C, Cooke KL, Huang W, and Levin SA (1989b) On the role of long incubation

periods in the dynamics of acquired immunodeficiency syndrome (AIDS). Part 2: Multiple group models. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 200–217.

Castillo-Chavez C, Cooke K, Huang W, and Levin SA (1989c) The role of long periods of infectiousness in the dynamics of acquired immunodeficiency syndrome (AIDS). In C Castillo-Chavez, SA Levin, and C Shoemaker (eds.): Mathematical Approaches to Problems in Resource Management and Epidemiology. Lecture Notes in Biomathematics 81. Berlin: Springer-Verlag, pp. 177–189.

Castillo-Chavez C, Cooke K, Huang W, and Levin SA (1989d) Results on the dynamics for models for the sexual transmission of the human immunodeficiency virus. Appl. Math. Lett. *2:*327–331.

Castillo-Chavez C, Hethcote HW, Andreasen V, Levin SA, and Liu WM (1988) Cross-immunity in the dynamics of homogeneous and heterogeneous populations. In L Gross, TG Hallam, and SA Levin (eds.): Mathematical Ecology. Proceedings, Autumn Course Research Seminars, Trieste 1986. Singapore: World Scientific Publications, pp. 303–316.

Castillo-Chavez C, Hethcote HW, Andreasen V, Levin SA, and Liu WM (1989e) Epidemiological models with age structure, proportionate mixing, and cross-immunity. J. Math. Biol. *27:*233–258.

Castillo-Chavez C, Levin SA, and Shoemaker CA (eds.) (1989f) Mathematical Approaches to Problems in Resource Management and Epidemiology. Lecture Notes in Biomathematics 81. Berlin: Springer-Verlag.

Centers for Disease Control (1987) Update: Acquired Immunodeficiency Syndrome—United States. MMWR *36:*522–526.

Centers for Disease Control (1989) Update: Acquired Immunodeficiency Syndrome—United States, 1981–1988. MMWR *38:*229–236.

Cliff AD and Haggett P (1980) Geographical aspects of epidemic diffusion in closed communities. In N. Wrigley (ed.): Statistical Applications in the Spatial Sciences. London: Pion, pp. 5–44.

Cliff AD and Haggett P (1984) Island epidemics. Sci. Am. *250:*138–147.

Cliff AD, Haggett P, Ord JK, Bassett K, and Davies RB (1975) Elements of Spatial Structure: A Quantitative Approach. Cambridge: Cambridge University Press.

Cliff AD, Haggett P, Ord JK, and Versey GR (1981) Spatial Diffusion: An Historical Geography of Measles Epidemics in an Island Community. Cambridge: Cambridge University Press.

Cliff AD and Murray JD (1977) A stochastic model for measles epidemics in a multi-region setting. Trans. Inst. Br. Geogr. NS *2:*158–174.

Cockburn TA (1971) Infectious diseases in ancient populations. Curr. Anthropol. *12:*45–62.

Cooke KL and Yorke JA (1972) Equations modelling population growth, economic growth, and gonorrhea epidemiology. In L Weiss (ed.): Ordinary Differential Equations. New York: Academic Press.

Cooke KL and Yorke JA (1973) Some equations modelling growth processes and gonorrhea epidemics. Math. Biosci. *16:*75–101.

Daniels HE (1975) The deterministic spread of a simple epidemic. In J Gani (ed.): Perspectives in Probability and Statistics. London: Academic Press, pp. 373–386.

DeGruttola V and Lagakos S (1989) Epidemic models, empirical studies, and uncertainty. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 38–57.

DeGrutolla V and Mayer KH (1988) Assessing and modeling heterosexual spread of the Human Immunodeficiency Virus in the United States. Rev Infect Dis *10:*138–150.

Diekmann O (1978) Thresholds and travelling waves for the geographical spread of infection. J. Math. Biol. *6:*109–130.

Dietz K (1975) Transmission and control of arbovirus diseases. In KL Cooke (ed.): Epidemiology. Philadelphia: Society for Industrial and Applied Mathematics, pp. 104–121.

Dietz K (1980) Models for vector-borne parasitic diseases. In C Barigozzi (ed.): Vito Volterra Symposium on Mathematical Models in Biology, Lecture Notes in Biomathematics 39. Berlin: Springer-Verlag, pp. 264–277.

Dietz K (1982) Overall population patterns in the transmission cycle of infectious disease agents. In RM Anderson and RM May (eds.): Population Biology of Infectious Diseases. New York: Springer-Verlag, pp. 87–102.

Dietz K (1988a) Density-dependence in parasite transmission dynamics. Parasitol. Today 4: 91–97.

Dietz K (1988b) Mathematical models for transmission and control of malaria. In WH Wernsdorfer and Sir I McGregor (eds.): Malaria: Principles and Practices of Malariology, Volume Two. Edinburgh: Churchill Livingstone, pp. 1091–1133.

Dietz K (1988c) On the transmission of HIV. Math. Biosci. *90:*397–414.

Dietz K (1988d) The first epidemic model: A historical note on P.D. E'nko. Aust. J. Statist. *30A:* 56–65.

Dietz K and Hadeler KP (1988) Epidemiological models for sexually transmitted diseases. J. Math. Biol. *26:*1–25.

Dietz K and Schenzle D (1985) Mathematical models for infectious disease statistics. In AC Atkinson and SE Fienberg (eds.): A Celebration of Statistics: The ISI Centenary Volume. New York: Springer-Verlag, pp. 167–204.

Dietz K, Molineaux L, and Thomas A (1974) A malaria model tested in the African savannah. Bull. WHO *50:*347–357.

Dutertre J (1976) Etude d'un modèle epidemiologique appliqué au paludisme. Ann. Soc. Belge Med. Trop. *56:*127–141.

Dye C and Hasibeder G (1986) Mosquito-borne disease dynamics: control of flies which bite some people more frequently than others. Trans. R. Soc. Trop. Med. Hyg. *80:*69–77.

Edman J, Day J, and Walker E (1985) Vector-host interplay—factors affecting disease transmission. In LP Lounibos, JR Rey, and JH Frank (eds.): Ecology of Mosquitoes. New York: Chapman & Hall, pp. 273–285.

Elderkin RH, Berkowitz DP, Farris FA, Gunn CF, Hickernell FJ, Kass SN, Mansfield FI, and Taranto RG (1977) On the steady state of an age dependent model for malaria. In V Lakshmikantham (ed.): Nonlinear Systems and Applications. New York: Academic Press, pp. 491–512.

Elveback LR, Fox JP, Ackerman E, Langworthy A, Boyd M, and Gatewood L (1976) An influenza simulation model for immunization studies. Am. J. Epidemiol. *103:*152–165.

E'nko PD (1889) The epidemic course of some infectious diseases. Vrach. St. Petersburg *10:*1008–1010, 1039–1042, 1061–1063. (in Russian)

Feldstein MS, Piot MA, and Sundaresan TK (1973) Resource allocation model for public health planning: a case study of tuberculosis control. Bull WHO [Suppl.] *48:*3–108.

Fine P (1982) Applications of mathematical models to the epidemiology of influenza: a critique. In P Selby (ed.): Influenza Models. Lancaster: MTP Press Limited, pp. 15–81.

Fredrickson AG (1971) A mathematical theory of age structure in sexual populations: random mating and monogamous marriage models. Math. Biosci. *20:*117–143.

Garrett-Jones C (1964) The human blood index of malaria vectors in relation to epidemiological assessment. Bull. WHO *30:*241–261.

Greenwood M (1931) On the statistical measure of infectiousness. J. Hyg. (Camb.) *31:*336–351.

Gupta S, Anderson RM, and May RM (1989) Networks of sexual contacts: Implications for the pattern of spread of HIV. AIDS *3:*807–817.

Haber M, Longini IM Jr, and Cotsonis GA (1988) Models for the statistical analysis of infectious disease data. Biometrics *44:*163–173.

Haggett P (1972) Contagious processes in a planar graph: an epidemiological application. In ND McGlashan (ed.): Medical Geography. London: Methuen, pp. 307–324.

Haggett P (1976) Hybridizing alternative models of an epidemic diffusion process. Econ. Geog. *52:* 136–146.

Haggett P (1982) Building geographic components into epidemiological models. In P Selby (ed.): Influenza Models: Prospects for Development and Use. Lancaster: MTP Press, pp. 203–212.

Halloran EM, Struchiner CJ, and Spielman A (1989) Modeling malaria vaccines II: population effects of stage-specific malaria vaccines dependent on natural boosting. Math. Biosci. *94:*115–149.

Hamer WH (1906) Epidemic disease in England. Lancet *1:*733–739.

Hasibeder G and Dye C (1988) Population dynamics of mosquito-borne disease: persistence in a completely heterogeneous environment. Theor. Pop. Biol. *33:*31–53.

Healy MJR and Tillett HE (1988) Short-term extrapolation of the AIDS epidemic. J. R. Statist. Soc. [A]*151:*50–61.

Hethcote HW (1988) Optimal ages of vaccination for measles. Math. Biosci. *89:*29–52.

Hethcote HW (1989) A model for HIV transmission and AIDS. In C Castillo-Chavez, SA Levin, and C Shoemaker (eds.): Mathematical Approaches to Problems in Resource Management and Epidemiology. Lecture Notes in Biomathematics 81. Berlin: Springer-Verlag, pp. 164–176.

Hethcote HW and Van Ark JW (1987) Epidemiological models for heterogeneous populations: proportionate mixing, parameter estimation and immunization programs. Math. Biosci. *28:*335–356.

Hethcote HW and Yorke JA (1984) Gonorrhea Transmission and Control. Lecture Notes in Biomathematics 56. New York: Springer-Verlag.

Hethcote HW, Yorke JA, and Nold A (1982) Gonorrhea modeling: A comparison of control methods. Math. Biosci. *58:*93–109.

Hope Simpson RE and Sutherland I (1954) Does influenza spread within the household? Lancet *1:*721–726.

Hoppensteadt F (1974) An age dependent epidemic model. J. Franklin Inst. *297:*325–333.

Hyman JM and Stanley EA (1988) Using mathematical models to understand the AIDS epidemic. Math. Biosci. *90:*415–474.

Hyman JM and Stanley EA (1989) The effect of social mixing patterns on the spread of AIDS. In C Castillo-Chavez, SA Levin, and C Shoemaker (eds.): Mathematical Approaches to Problems in Resource Management and Epidemiology, Lecture Notes in Biomathematics 81. Berlin: Springer-Verlag, pp. 190–219.

Isham V (1988) Mathematical modelling of the transmission dynamics of HIV infection and AIDS: a review. J. R. Statist. Soc. [A]*151:*5–30.

Jacquez JA (1987) A note on chain-binomial models of epidemic spread: What is wrong with the Reed-Frost formulation? Math. Biosci. *87:*73–82

Jacquez JA, Simon CP, and Koopman J (1989) Structured mixing: heterogeneous mixing by the definition of mixing groups. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 301–315.

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

Jorde LB, Pitkänen K, Mielke JH, Fellman JO, and Eriksson AW (1989a) Historical epidemiology of smallpox in Kitee, Finland. In AC Swedlund and G Armelagos (eds.): The Health and Disease of Populations in Transition. South Hadley, MA: Bergin & Garvey. (in press.)

Jorde LB, Pitkänen KJ, and Mielke JH (1989b) Predicting smallpox epidemics: a statistical analysis of two Finnish populations. Am. J. Hum. Biol. *1:*621–629.

Kaplan EH (1989a) What are the risks of risky sex? Modeling the AIDS epidemic. Oper. Res. *37:* 198–209.

Kaplan EH (1989b) Can bad models suggest good policies? Sexual mixing and the AIDS epidemic. J. Sex Res. *26:*301–314.

Kaplan EH (1989c) Needles that kill: Modeling human immunodeficiency virus transmission via shared drug injection equipment in shooting galleries. Rev. Infect. Dis. *11:*289–298, 672.

Kaplan EH (1990) Modeling HIV infectivity: Must sex acts be counted? J. AIDS *3:*55–61.

Kaplan EH (1991) Worst case analysis of sexual mixing models of HIV transmission. J. Sex Res. (in press)

Kaplan EH, Cramton PC, and Paltiel AD (1989) Nonrandom mixing models of HIV transmission. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 218–241.

Kaplan EH and Lee YS (1990) How bad can it get? Bounding worst case endemic heterogeneous mixing models of HIV/AIDS. Math. Biosci. *99:* 157–180.

Karon JM, Devine OJ, and Morgan WM (1989) Predicting AIDS incidence by extrapolating from

recent trends. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 58–78.
Kemper JT (1981) Error sources in the evaluation of secondary attack rates. Am. J. Epidemiol. *112:* 457–464.
Kendal AP, Joseph JM, Kobayashi G, Nelson D, Reyes CR, Ross MR, Sarandria JL, White R, Woodall DF, Noble GR, and Dowdle WR (1979) Laboratory-based surveillance of influenza virus in the United States during the winter of 1977–1978. Am. J. Epidemiol. *110:*449–461.
Kendall DG (1949) Stochastic processes and population growth. R. Statist. Soc. [B]*2:*230–264.
Kendall DG (1965) Mathematical models of the spread of infection. In DG Kendall (ed.): Mathematics and Computer Science in Biology and Medicine. London: H.M.S.O., pp. 213–225.
Kermack WO and McKendrick AG (1927) Contributions to the mathematical theory of epidemics, part I. Proc. R. Soc. [A]*115:*700–721.
Kießling D, Stannat S, Schedel I, and Deicher H (1986) Überlegungen und hochrechnungen zur epidemiologie des "acquired immunodeficiency syndrome" in der Bundesrepublik Deutschland. Infection *14:*217–221.
Kingsolver JG (1987) Mosquito host choice and the epidemiology of malaria. Am. Nat. *130:*811–827.
Knox EG (1986) A transmission model for AIDS. Eur. J. Epidemiol. *2:*165–177.
Koopman J, Simon CP, Jacquez JA, and Park T (1989) Selective contact within structured mixing groups: application to the analysis of HIV transmission risk from oral and anal sex. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 316–348.
Koopman J, Simon C, Jacquez J, Joseph J, Sattenspiel L, and Park T (1988) Sexual partner selectiveness effects on homosexual HIV transmission dynamics. J. AIDS *1:*486–504.
Koplan JP, Schoenbaum SC, Weinstein MC, and Fraser DW (1979) Pertussis vaccine—an analysis of benefits, risks and costs. N. Engl. J. Med. *301:* 906–911.
Kostitzin VA (1934) Symbiose, Parasitisme et Évolution (Étude Mathématique). Paris: Hermann.
Kostitzin VA (1978) Symbiosis, parasitism and evolution. In FM Scudo and JR Ziegler (eds.): The Golden Age of Theoretical Ecology: 1923–1940. Berlin: Springer-Verlag, pp. 369–408.
Lajmanovich A and Yorke JA (1976) A deterministic model for gonorrhea in a nonhomogeneous population. Math. Biosci. *28:*221–236.
Layne SP, Spouge JL, and Dembo M (1989) Measuring HIV infectivity. In C Castillo-Chavez (ed.):Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 80–110.
Levin SA, Hallam TG, and Gross LJ (eds.) (1989) Applied Mathematical Ecology. Berlin: Springer-Verlag.
Longini IM Jr (1988) A mathematical model for predicting the geographic spread of new infectious agents. Math. Biosci. *90:*367–383.
Longini IM Jr and Koopman JS (1982) Household and community transmission parameters from final distributions of infections in households. Biometrics *38:*115–126.
Longini IM Jr, Ackerman E, and Elveback LR (1978) An optimization model for influenza A epidemics. Math Biosci. *38:*141–157.
Longini IM Jr, Clark WS, Haber M, and Horsburgh R Jr (1989) The stages of HIV infection: waiting times and infection transmission probabilities. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 111–137.
Longini IM Jr, Fine PEM, and Thacker SB (1986) Predicting the global spread of new infectious agents. Am. J. Epidemiol. *123:*383–391.
Longini IM Jr, Koopman JS, Monto AS, and Fox JP (1982) Estimating household and community transmission parameters for influenza. Am. J. Epidemiol. *115:*736–751.
Longini IM Jr, Seaholm SK, Ackerman E, Koopman JS, and Monto AS (1984) Simulation studies of influenza epidemics: assessment of parameter estimation and sensitivity. Int. J. Epidemiol. *13:* 496–501.
Macdonald G (1965) The dynamics of helminth infections with special reference to schistosomes. Trans. R. Soc. Trop. Med. Hyg. *59:*489–506.
Maia J de OC (1952) Some mathematical developments on the epidemic theory formulated by Reed and Frost. Hum. Biol. *24:*167–200.
May RM (1986) Population biology of microparasitic infections. In TG Hallam and SA Levin (eds.-):Mathematical Ecology. Berlin: Springer-Verlag, pp. 405–442.
May RM and Anderson RM (1979) Population biology of infectious diseases, Part II. Nature *280:* 455–461.
May RM and Anderson RM (1987) Transmission dynamics of HIV infection. Nature *326:*137–142.
May RM and Anderson RM (1988) The transmission dynamics of the human immunodeficiency virus (HIV). Philos. Trans. R. Soc. Lond. [Biol] *321:*565–607.
May RM, Anderson RM, and McLean AR (1988) Possible demographic consequences of HIV/AIDS epidemics. I. Assuming HIV infection always leads to AIDS. Math. Biosci. *90:*475–505.
May RM, Anderson RM, and McLean AR (1989) Possible demographic consequences of HIV/AIDS epidemics. II. Assuming HIV infection does not necessarily lead to AIDS. In C Castillo-Chavez, SA Levin, and C Shoemaker (eds.): Mathematical Approaches to Problems in Resource Management and Epidemiology, Lecture Notes in Biomathematics 81. Berlin: Springer-Verlag, pp. 220–247.
McGrath JW (1988) Social networks of disease spread in the lower Illinois valley: A simulation approach. Am. J. Phys. Anthropol. *77:*483–496.
McKendrick AG (1926) Applications of mathematics to medical problems. Proc. Edinburgh Math. Soc. *44:*98–130.
Meegama SA (1986) The mortality transition in Sri Lanka. In: Determinants of Mortality Change and Differentials in Developing Countries, Population Studies No. 94. New York: United Nations, pp. 5–32.
Mercer AJ (1985) Smallpox and epidemiological-demographic change in Europe: The role of vaccination. Popul. Stud. *40:*129–145.
Mielke JH, Jorde LB, Trapp PG, Anderton DL, Pitkänen K, and Eriksson AW (1984) Historical ep-

idemiology of smallpox in Åland, Finland: 1751–1890. Demography *21*:271–295.
Milner GR (1980) Epidemic disease in the post-contact Southeast: A reappraisal. Mid. Cont. J. Arch. *5*:39–56.
Mode CJ, Gollwitzer HE, and Herrmann N (1988) A methodological study of a stochastic model of an AIDS epidemic. Math. Biosci. *92*:201–229.
Molineaux L (1985) The pros and cons of modelling malaria transmission. Trans. R. Soc. Trop. Med. Hyg. *79*:743–747.
Molineaux L and Gramiccia G (1980) The Garki Project: Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa. Geneva: WHO.
Molineaux L, Dietz K, and Thomas A (1978) Further epidemiological evaluation of a malaria model. Bull. WHO *50*:565–571.
Morris M (1989) Networks and diffusion: an application of loglinear models to the population dynamics of disease. Unpublished Ph.D. dissertation, University of Chicago.
Moser MR, Bender TR, Margolis HS, Noble GR, Kendal AP, and Ritter DG (1979) An outbreak of influenza aboard a commercial airliner. Am. J. Epidemiol. *110*:1–6.
Muirhead-Thomson RC (1951) The distribution of anopheline mosquito bites among different age groups—A new factor in malaria epidemiology. Br. Med. J. *1*:1114–1117.
Murray JD (1989) Mathematical Biology. New York: Springer-Verlag.
Nedelman J (1984a) A negative binomial model for sampling mosquitoes in a malaria survey. Biometrics *39*:1009–1020.
Nedelman J (1984b) Inoculation and recovery rates in the malaria model of Dietz, Molineaux, and Thomas. Math. Biosci. *69*:209–233.
Nedelman J (1985) Introductory review: some new thoughts about some old malaria models. Math. Biosci. *73*:159–182.
Nold A (1980) Heterogeneity in disease-transmission modeling. Math. Biosci. *52*:227–240.
Pease CM (1987) An evolutionary epidemiological mechanism, with applications to type A influenza. Theor. Pop. Biol. *31*:422–452.
Pickering J, Wiley JA, Padian NS, Lieb LE, Echenberg DG, and Walker J (1986) Modeling the incidence of acquired immunodeficiency syndrome (AIDS) in San Francisco, Los Angeles, and New York. Math. Modeling *7*:661–688.
Pitkänen KJ, Mielke JH, and Jorde LB (1989) Smallpox and its eradication in Finland: Implications for disease control. Popul. Stud. *43*:95–111.
Ramenofsky AF (1987) Vectors of Death. Albuquerque: University of New Mexico Press.
ReVelle C and Male J (1970) A mathematical model for determining case finding and treatment activities in tuberculosis control programs. Annu. Rev. Respir. Dis. *102*:403–411.
ReVelle CS, Lynn WR, and Feldmann F (1967) Mathematical models for the economic allocation of tuberculosis control activities in developing nations. Annu. Rev. Respir. Dis. *96*:893–909.
Ross R (1911) The Prevention of Malaria, 2nd ed. London: Murray.
Ross R (1915) Some a priori pathometric equations. Br. Med. J. *1*:546–547.
Rvachev LA and Longini IM Jr (1985) A mathematical model for the global spread of influenza. Math. Biosci. *75*:3–22.
Sartwell P (1950) The distribution of incubation periods of infectious disease. Am. J. Hyg. *51*:310–318.
Sattenspiel L (1987) Population structure and the spread of disease. Hum. Biol. *59*:411–438.
Sattenspiel L (1989) The structure and context of social interactions and the spread of HIV. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer Verlag, pp. 242–259.
Sattenspiel L and Castillo-Chavez C (1990) Environmental context, social interactions, and the spread of HIV. Am. J. Hum. Biol. *2*:397–417.
Sattenspiel L and Simon CP (1988) The spread and persistence of infectious diseases in structured populations. Math. Biosci. *90*:341–366.
Sattenspiel L, Koopman J, Simon C, and Jacquez J (1990) The effects of population structure on the spread of the HIV infection. Am. J. Phys. Anthropol. *82*:421–429.
Schaffer WM and Kot M (1985) Nearly one dimensional dynamics in an epidemic. J. Theor. Biol. *112*:403–427.
Schaffer WM and Kot M (1986) Chaos in ecological systems: The coals that Newcastle forgot. Tree *1*:58–63.
Schenzle D (1985) Control of virus transmission in age-structured populations. In V Capasso, E Grosso, and SL Paveri-Fontana (eds.): Mathematics in Biology and Medicine, Lecture Notes in Biomathematics 57. Berlin: Springer-Verlag, pp. 171–178.
Schoenbaum SC, Hyde JN Jr, Bartoshesky L, and Crampton K (1976a) Benefit-cost analysis of rubella vaccination policy. N. Engl. J. Med. *294*: 306–310.
Schoenbaum SC, McNeill BJ, and Kavet J (1976b) The swine-influenza decision. N. Engl. J. Med. *295*:759–765.
Schwager SJ, Castillo-Chavez C, and Hethcote HW (1989) Statistical and mathematical approaches in HIV/AIDS modeling: a review. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 2–36.
Shidrawi GR, Boulzaquet JR, Ashkar TS, and Brøgger S (1974) Nightbait collection: the variation between persons used as collector baits. Unpublished WHO Technical Note No. 17, MPD/TN/74. *1*:9–18.
Soper HE (1929) Interpretation of periodicity in disease prevalence. J. R. Statist. Soc. *92*:34–73.
Spicer CC (1979) The mathematical modelling of influenza epidemics. Br. Med. Bull. *35*:23–28.
Struchiner CJ, Halloran ME, and Spielman A (1989) Modeling malaria vaccines I: New uses for old ideas. Math. Biosci. *94*:87–113.
Sugiyama H (1960) Some statistical contributions to the health sciences. Osaka City Med. J. *6*:141–158.
Sugiyama H (1961) Some statistical methodologies for epidemiological research of medical sciences. Bull. Int. Statist. Inst. *38*:137–151.
Thieme HR and Castillo-Chavez C (1989) On the role of variable infectivity in the dynamics of the human immunodeficiency virus epidemic. In C Castillo-Chavez (ed.): Mathematical and Statisti-

cal Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 157–176.
Travis CC and Lenhart SM (1987) Eradication of infectious diseases in heterogeneous populations. Math. Biosci. *83:*191–198.
Upham S (1986) Smallpox and climate in the American Southwest. Am. Anthropol. *88:*115–128.
Waaler HT (1968) A dynamic model for the epidemiology of tuberculosis. Am. Rev. Respir. Dis. *98:* 591–600.
Waaler HT and Piot MA (1969) The use of an epidemiological model for estimating the effectiveness of tuberculosis control measures. Bull. WHO *41:*75–93.
Waldstätter R (1989) Pair formation in sexually-transmitted diseases. In C Castillo-Chavez (ed.): Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomathematics 83. Berlin: Springer-Verlag, pp. 260–274.
Webb GF (1985) Theory of Nonlinear Age-dependent Population Dynamics. New York: Dekker.
Wiesenfeld SL (1967) Sickle-cell trait in human biological and cultural evolution. Science *157:* 1134–1140.
Wiley JA and Herschkorn SJ (1989) Homosexual role separation and AIDS epidemics: Insights from elementary models. J. Sex Res. *4:*434–449.
Wilkie AD (1988) An actuarial model for AIDS. J. R. Statist. Soc. [A]*151:*35–39.
Willems JS and Sanders CR (1981) Cost-effectiveness and cost-benefit analyses of vaccines. J. Infect. Dis. *144:*486–493.
Yamamoto K (1959) A theoretical epidemiological study on the mode of infection of influenza in the household. J. Osaka City Med. Center *9:*2179–2190.
Yorke JA, Hethcote HW, and Nold A (1978) Dynamics and control of the transmission of gonorrhea. Sex. Transm. Dis. *5:*51–56.