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Economic incentives and mathematical models of disease

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ABSTRACT. The fields of epidemiological disease modeling and economics have tended to work independently of each other despite their common reliance on the language of mathematics and exploration of similar questions related to human behavior and infectious disease. This paper explores the benefits of incorporating simple economic principles of individual behavior and resource optimization into epidemiological models, reviews related research, and indicates how future cross-discipline collaborations can generate more accurate models of disease and its control to guide policy makers.

1. Introduction

Infectious diseases are responsible for a quarter of all deaths in the world annually, the vast majority occurring in low- and middle-income countries (Laxminarayan *et al.*, 2006a). Even when infections do not kill, they reduce the quality of life for hundreds of millions of people and retard economic growth. In low-income countries in particular, a vicious cycle sets in: infectious disease leads to poverty, which increases the risk for disease. In high-income countries, preventable infectious diseases like influenza and hospital-acquired bacterial infections remain important causes of death and disability.

Interest in the study of infectious diseases by economists has been motivated not only by their economic impact but also by a desire to understand how individuals respond to the risk of infection and how best

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to design and allocate resources for public health programs of prevention and treatment. Despite their common use of mathematics, and pursuit of similar questions, rarely have economists, mathematical epidemiologists, and biologists collaborated in understanding how diseases evolve and spread.

In this paper, we review trends in mathematical disease models, acknowledging that a lot is known about modeling disease dynamics and control by scaling up from individual infections to epidemics in populations. The models include such factors as the spatial structure and heterogeneity of host populations and the topology of contacts between infected and susceptible individuals. We discuss the interplay between human behavior and economic incentives and suggest three important directions for future collaborations that benefit many people at no cost to themselves: (i) incorporating assumptions of rational behavior among individuals and policy makers in managing the risks of infection; (ii) considering externalities, and the broader, sometimes unforeseen consequences of individual actions; and (iii) taking into account global disease commons, such as the eradication of a disease or the minimization of the risks of antibiotic resistance. We conclude with a discussion where we suggest that greater collaboration across the two fields could generate more useful models to guide policy as well as enhance understanding of how diseases and humans interact.

2. Mathematical models – achievements and failings

Since the eighteenth century, scientists have been using mathematical models of infectious diseases to inform public policy. In 1766, Bernoulli used smallpox mortality projections to argue for increased 'inoculation', despite a lack of understanding of how the disease infected and killed people (Blower and Bernoulli, 2004). In 1854, systematic observations led John Snow to identify a single water pump as the source of a cholera outbreak, thereby contributing to the development of epidemiology as a science (Snow, 1855). In 1882, Koch's postulates established formal criteria to show that specific microbes caused specific diseases, after which scientists identified the bacterial and parasitic causes of many infections and began to understand how infectious agents spread (Walker *et al.*, 2006). By the beginning of the twentieth century, mathematical models had been developed for measles (Hamer, 1906) and malaria (Ross, 1910), and Kermack and McKendrick (1927) had established the mathematical theory of epidemics. By the 1950s, mathematical models had explored the stochastic aspects of infectious diseases, especially the stochastic fadeout of measles, and the critical factor of community size in sustaining an epidemic (Bartlett, 1956, 1957).

The second half of the twentieth century saw further refinements in mathematical models for the invasion and persistence of human pathogens (Anderson and May, 1991; Grenfell *et al.*, 2002). Similar techniques were applied to the study of the spread of animal and plant diseases, both in agricultural and natural landscapes (Carlsson-Granér and Thrall, 2002; Gilligan, 2002; Grenfell and Dobson, 1995; Keeling *et al.*, 2004; Smith *et al.*, 2002). As a result, a theory emerged of how epidemics spread and how control measures should be deployed that can be applied to a wide range of pathogens, host populations, and environments. The underlying

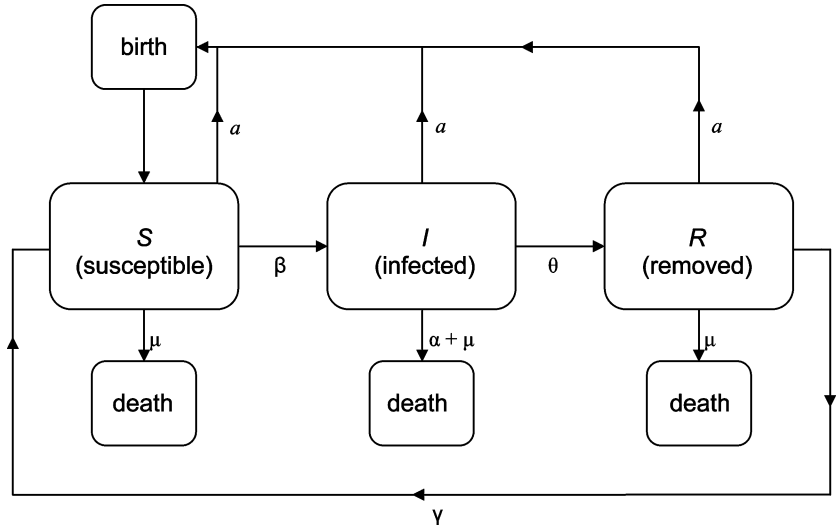

Figure 1. *Schematic representation of an SIR model.*
Note: The SIR model describes the dynamic interaction between a directly transmitted microparasite and its host population, as hosts flow between the different states of the S (susceptible), I (infected), and R (removed – dead or recovered) classes. Hosts reproduce at a per capita rate of a and die at a per capita rate of μ. Infected hosts experience an additional disease-induced death rate α in addition to the background mortality rate. Susceptible hosts become infected at rate βI, the transmission rate, which arises due to contact between susceptible and infected individuals. Infected individuals recover at rate θ (duration $= 1/\theta$) and removed individuals become susceptible again at rate γ (duration $= 1/\gamma$), in diseases where recovery is not possible θ would be 0. More complex models may add additional classes, but the underlying concept is the same.

models are often formulated as 'MSEIR' models (Hethcote, 2000) in which the epidemiological status of an individual in the host population is characterized as one of several states: M is the class of newborns who retain some protective maternal antibodies, S is the susceptible class, E is exposed (i.e. infected but not infectious), I is infectious, and R is removed (dead or recovered) (see figure 1). Control treatments are then modeled by their quantitative effects upon epidemiological parameters, notably transmission rates, and infectious and latent periods, or by introducing additional transitions, as when a vaccination program switches individuals from a susceptible to a removed class (Anderson and May, 1991).

Epidemiological research has increasingly focused on introducing greater biological realism into models to refine understanding of the invasion and persistence of endemic, exotic, emerging, and re-emerging diseases. In general, most attention has been paid to spatial dynamics, heterogeneity, stochasticity, and transient dynamics. This allows analysis and comparison of different strategies of infection control as a disease spreads through spatially structured populations such as villages, towns, or cities, taking into account the uncertainty in transmission dynamics and the effectiveness

of control. Analyses of stochasticity also allows epidemiologists to predict times to extinction (Keeling *et al.*, 2001) and times to invasion (Ferguson *et al.*, 2003) as well as to determine the probability density functions for risk of infection and failure of control (Gibson *et al.*, 1999). With some notable exceptions arising from economic and control theory literature (see e.g. Forster and Gilligan, 2007; Laxminarayan and Brown, 2001; Goldman and Lightwood, 2002; Rowthorn and Brown, 2003; Sethi, 1974), surprisingly little attention has been paid to formal economic optimization that takes account of the costs of disease and control. Strikingly too, mathematical epidemiologists seldom consider discount rates within cost functions and so consider the costs of infection and control today to be the same as they will be in the future. Economists, for their part, frequently ignore epidemic dynamics, treating disease models as if they were static and pay little heed to the spatial structure of host populations.

Spatial structure in epidemiological modeling currently explores structured metapopulations (Keeling and Gilligan, 2000; Smith *et al.*, 2005), individual-based networks, or spatial models (Dybiec *et al.*, 2004; Keeling, 2005). Structured metapopulations allow for computation of transit times before hosts move from one subpopulation to another; individual network models look at the contact topology around hosts, and explicit spatial models describe dispersal as a function of distance, called a dispersal kernel, with occasional long-distance mixing. All three types of models have consequences for the local and global control of disease. Despite the insights drawn from these models, many strategies, especially in agriculture but also for human disease, are focused on locally eliminating infection without considering the global consequences of these practices. Thus they promote individual benefit over public good. In the end, such strategies, typified by the promotion of drug and pesticide resistance through overuse, are counterproductive since they lead to ever-escalating costs to develop new pesticides, drugs or genetically resistant crop varieties.

Behavioral considerations

Despite the important advances described above, most mathematically based epidemiological models regard hosts in epidemics the same way that chemists regard molecules in a chemical reaction – freely mixing and incapable of change. For example, the rate of contact (β – see figure 1) between infected and susceptible individuals in many simple and some not-so-simple models is treated as a constant that is independent of the number and often the density of infected individuals. Only recently, following the emergence of HIV/AIDS and increased antibiotic resistance, have more complex human behaviors, including heterogeneous sexual mixing rates (Hethcote and Yorke, 1984; Blower and McLean, 1991), rational responses to economic incentives (Smith *et al.*, 2005; Phillipson and Posner, 1993), more realistic descriptions of risk-taking behavior (Anderson and May, 1991; Blower and McLean, 1994; Blower *et al.*, 2000, 2002; Hyman and Li, 1997; Del Valle *et al.*, 2005), and the evolution of infectious agents themselves (Dieckmann, 2002; Anderson and May, 1991), been incorporated into mathematical models.

The spread of an infectious disease is a population-level phenomenon, but decisions to prevent or treat a disease are often made by individuals who may change their behavior over the course of an epidemic, especially if their perception of risk changes – their decisions will then have population-level consequences. One reason for the lack of attention to behavioral dynamics or economic incentives in disease models may be because biologists have focused on the biology of infection and immunity, especially in relation to diseases like malaria and tuberculosis, where the complexity of the parasite life-cycle and bacterial characteristics were thought to be significant drivers of an epidemic. In fact, Anderson and May's (1991) review, arguably the most complete survey of mathematical epidemiology through the 1980s, does not list human behavior in the index and only briefly discusses heterogeneity in sexual habits related to HIV/AIDS. Even in models of HIV/AIDS and other sexually transmitted diseases, where the risk of infection is driven by sexual behavior, mathematical epidemiologists have placed more emphasis on describing sexual contact networks and the dynamics and control of infectious diseases on those networks rather than the underlying incentives and other determinants that lead to the formation and evolution of those networks through individual choices to engage in risky behavior (Koopman *et al.*, 1988; Koopman *et al.*, 1991; Klovdahl *et al.*, 1994; Kretzschmar *et al.*, 1996; Stigum *et al.*, 1997; Wallace, 1991).

Another reason may be relatively poor communication across disciplines. This may reflect early separation in training for careers in the natural versus the social sciences, which is further reinforced by largely separate literatures. Consequently, incentives and behavior have routinely been omitted from disease models, while economic models for disease dynamics rarely consider spatial structures of susceptible populations or stochasticity in transmission dynamics and survival, and many apply a cost–benefit analysis to systems undergoing transient dynamics that are nevertheless assumed to be in equilibrium (Geoffard and Philipson, 1997; Kremer, 1996).

Incorporating behavior into epidemiological disease models can enhance a model's utility in evaluating control measures. The field of epidemiology has devoted substantial effort to understanding the impact of human practices and behavior on the spread of disease (see Tanaka *et al.*, 2002 for a short discussion of the literature) but this understanding has not always made its way into mathematical models. Important exceptions include, Blower and McLean (1994), Blower *et al.* (2000), Blower *et al.* (2002), Blythe *et al.* (1991), Brauer *et al.* (1992), Hethcote *et al.* (1991), Hyman and Li (1997), Del Valle *et al.* (2005), Boni and Feldman (2005), Tanaka *et al.* (2002), and Velasco-Hernandez and Hsieh (1994). Generally, however, these models have dealt with sexually transmitted diseases, and most models of disease still tend to ignore the impacts of changes in behavior (see figure 2 for an illustration of how behavior can impact the dynamics of traditional models of disease). Yet, human behavior is relevant in mathematical disease models for non-sexually transmitted diseases as well. For example, mass spraying to reduce malaria transmission can reduce the irritating effects of biting by nuisance mosquitoes and so lead to reduced personal use of bed-nets. Models for control that ignore such behavioral feedback can seriously

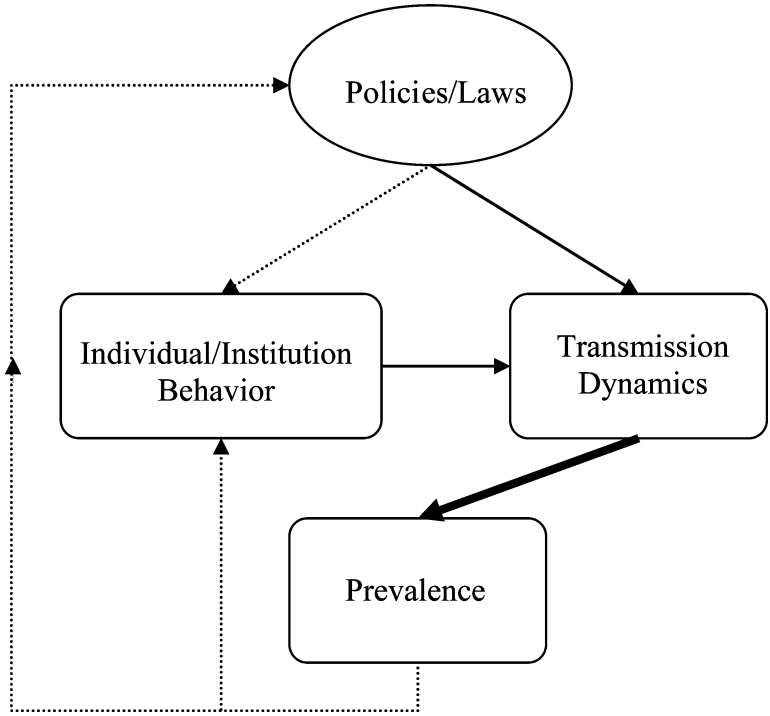

Figure 2. *Mathematical models of disease and prevalence dependent behavior responses. Note:* Mathematical models of disease have generally examined how transmission dynamics can impact the prevalence of disease (dark line above – see Anderson and May, 1991), where dynamics are based on structural factors such as demographics, social networks, and socioeconomic factors (not pictured) as well as prevailing laws/policies or, in the case of some mixing models, on differing segments of the population (medium lines above – see e.g. Klovdahl, 1994; Koopman *et al.*, 1988; Koopman *et al.*, 1991; Wallace, 1991). More recently, especially in the context of HIV/AIDS, models have included dynamic interactions between prevalence and individual behavior and policy/laws and the subsequent impact on transmission dynamics and prevalence (Blower and McLean, 1994; Blythe *et al.*, 1991, Hethcote *et al.*, 1991, Phillipson and Posner, 1993). These areas (dotted lines above), though, have generally not been explicitly modeled in mathematical models of disease.

miscalculate the benefits and costs of a policy by ascribing undue influence to some parameters and exaggerating or underestimating gains.

Economic considerations

Along with behavior, the inclusion of economic incentives into disease models can also enhance the policy relevance of models. Economic incentives are often used as policy levers in much the same way as direct interventions. Malaria transmission can be reduced by spraying to kill mosquitoes, by giving away bed-nets, or by subsidizing the cost

of nets. Each option raises a different set of policy issues depending on human behavior, the local vector ecology, and whether the measures are used singly or together. Without explicitly considering the incentives of individuals to protect themselves or seek treatment, it is difficult to compare the effectiveness and cost-effectiveness of different disease control interventions. For example, bed-nets only deter vectors that bite at night, not those that bite during the day, and their use is encouraged even in the presence of mosquitoes that do not transmit diseases. On the other hand, people are generally unwilling to use bed-nets when it is too hot to sleep indoors or under a net.[1] Choosing any intervention requires examining such factors as an understanding of the ecology of malaria transmission, consumer demand for bed-nets, and benefits from the reductions in transmission that accrue to non-bed-net users living among or near bed-net users. In short, an economic analysis that includes only purchasing behavior, and ignores the total benefit of bed-nets or the total benefits of mass spraying or other alternatives would be less helpful in informing policymaking. Similar principles apply to antibiotics, vaccines, and other control measures.

Although disease models are reliable representations of biological phenomena like immunity and transmissibility, they are often abstractions of policy and implementation reality. For example, disease models addressing antibiotic resistance often assume that antibiotics are all alike and recommend a heterogeneous mix – that is, all antibiotics should be used concurrently, so that the use of each drug reduces the fitness of a pathogen that is resistant to the others, relative to a completely sensitive pathogen (Bonhoeffer *et al.*, 1997). Antibiotics differ from one another, in several ways, however, including their toxicity, the number of pathogens that they can treat (i.e. whether they are broad- or narrow-spectrum), and efficacy. Laxminarayan and Brown (2001) propose thinking of antibiotics as natural resources, similar to forests or oil, and suggest that models of resource extraction may be helpful in understanding how to manage the effectiveness of antibiotics. The economically optimal solution may be to use antibiotics with the greatest effectiveness first. In addition, the standard medical practice of using the 'optimal' or 'single best' treatment for an infectious disease may not be the most cost-effective solution from a societal standpoint. Instead, it may be preferable to use a heterogeneous mix of drugs, taking into consideration not only their direct cost, but also the probability of resistance (Laxminarayan and Weitzman, 2002).

Economic costs are also often ignored in infectious disease models, even though imposing these additional constraints could alter conclusions. Returning to the antibiotics example, in the absence of economic considerations, treating different patients with a variety of antibiotics with unrelated genetic bases for resistance, rather than cycling through those

[1] In addition to host behavior, disease models should also incorporate the behavior of vectors. Mosquitoes, for example, can develop resistance to pesticides or evolve behaviors to avoid other preventive measures such as bed-nets (Mangel and Roitberg, 1995).

antibiotics, is considered the optimal strategy (Bergstrom *et al.*, 2004). However, including the costs of maintaining more than one antibiotic on the shelf, lost discounts from not using a single drug provider, costs associated with returning or disposing of expired drugs, and the extra time physicians need to learn and maintain knowledge on the use of multiple drugs could make cycling antibiotics a better strategy than heterogeneous use (Laxminarayan and Smith, 2006).

Many disease models limit their usefulness in formulating policy by assuming that an infection tomorrow is valued the same as an infection today, which is unrealistic. Discount rates are common in economic models but rare in epidemiological models (Anderson *et al.*, 1986; Park *et al.*, 2001). Consider for example a policy maker in 1990 determining how best to allocate resources in the fight against HIV. Models that did not discount the cost of future infections would have suggested policies that minimized the total number of infections, without taking account of the much higher cost, increased risk of death, shorter life spans, and increased stigmatism of infections in 1990. Forster and Gilligan (2007) have recently shown how the inclusion of a discount factor in an epidemiological model can drastically change the nature of an optimal strategy for disease control from one that switches between treating or not treating all infected individuals to switches in which it is optimal to treat only a proportion of infected individuals. Although determining what discount rate to use is a point of debate (see Severens and Milne, 2004; Lazaro, 2002; Torgerson and Raftery, 1999), it is important to recognize that technological change, inflation, the affluence of future generations, and even ethical concerns suggest an infection today is costlier than a similar infection a few years hence (see Viscusi, 1995, for a discussion).

3. Rational behavior and prevalence responsiveness

Mathematical epidemiology research has largely focused on modes of transmission of infection (Ferguson *et al.*, 2001; Riley *et al.*, 2003), and on scaling up from individual- to population-level behavior, using individual-based (or agent-based) models (Grenfell *et al.*, 2002; Kleczkowski *et al.*, 1997; Swinton *et al.*, 1999). However, few mathematically based model studies have explicitly addressed the problem of rational behavior at the individual level and its effects at the population level. Individual behavior is often considered exogenous – that is, unaffected by disease prevalence. However, studies indicate otherwise, in particular those of sexually transmitted diseases, but for other diseases as well. For example, an individual may choose to have unsafe sex or a doctor may prescribe antibiotics to someone without a confirmed bacterial infection. In both cases, the choice may be rational from the individual's point of view but undesirable from a societal perspective.

Threshold effects

Limiting the spread of a disease at the population level requires changing individual behavior, which in turn depends on what information individuals have about the level of risk. When risk is low, people will tend to ignore it. However, if the risk of infection is higher, individuals

are more likely to take preventive action. Moreover, the more transmissible the pathogen, the greater the incentive is to make personal investments for control. The converse is also true: if there is a lowered risk of disease, either through vaccination or because of lowered prevalence, individuals may increase their risk-taking behavior.

This effect is analogous to the introduction of safety regulations, such as seatbelts in cars. Peltzman (1975) demonstrated that the reduced cost of an accident in terms of expected injury and death from the use of seatbelts could lead people to drive with less caution. The resulting injuries to non-occupants and increased nonfatal crashes may offset some of the gains from the use of seatbelts. Peltzman (1987) found similar effects when examining prescription drugs and especially antibiotics. Regulation of drugs generally eliminated poorly manufactured and fraudulent drugs, thus reducing the likelihood that someone would take a medicine that was harmful to them. However, prescription-only drugs, which were introduced, were more likely to be stronger than non-prescription drugs. Thus, while people were less likely to consume harmful medicine (such as one contaminated with harmful substances), they were more likely to consume stronger, more potent pills, which if misused (purposely in the case of a suicide attempt, or unwittingly in the case of an accidental overdose) were more likely to cause harm, reducing to some extent the benefit of introducing regulation. Similarly, Peltzman (2001) observed that a child born today has essentially no risk of dying from many of the diseases that were scourges of this earth as recently as the 1940s. However, he suggests that this has led to a loosening of some constraints on behavior or an increase in other behaviors, such as suicides, homicides, and accident causing behavior, which carry other kinds of mortality risk and offset some of the gains made by the introduction of antibiotics.

In the case of a sexually transmitted disease, such as HIV/AIDS, the rate of sexual partner change may depend on the transmission rate of HIV (Philipson and Posner, 1993; Blythe *et al.*, 1991). Prevalence-dependent behavior introduces a crucial difference in the net secondary transmission rate compared with disease models that take behavior as exogenous. Under the latter assumption or if behavioral responses are assumed to be inelastic with respect to disease prevalence, the per capita risk of infection in the susceptible population increases as prevalence increases. In contrast, when behavior is endogenous and elastic, hosts can act to reduce their risks. If their responses are strong enough, they can reduce the average per capita risk and offset the increases in the risk of transmission associated with higher prevalence.

Kremer (1996) showed that differences in risk level between groups with high and low rates of partner change could drive prevalence-dependent behavior. Individuals with low rates of partner change substantially increase their risk of infection with an additional partner compared with high-risk individuals. Consequently, they will curtail their risky behavior more drastically than will high-risk individuals when they perceive an increase in risk. The reduced sexual activity in the low-risk group reduces the number of low-risk partners available to the high-risk group, increasing their risk, since a higher fraction of their sexual partners will also be

high-risk. Because of this increased risk, high-risk individuals will therefore decrease their rate of partner change even more.[2]

Prevalence-dependent models of disease transmission have important implications for the timing of public interventions. Geoffard and Philipson (1996) suggest that prevalence and public subsidies compete to induce protective behavior. In other words, if prevalence induces the same sort of protective behavior as public subsidies, the subsidies become irrelevant because people will choose to protect themselves when prevalence is high, regardless of the subsidy and subsidies may not be helpful at the times when they are typically applied.

The theory also suggests how the introduction of a vaccine may affect the spread of a disease. As the prevalence of a disease increases, people will demand to be vaccinated. As prevalence decreases, however, the incentive, and thus demand, will slacken and allow the susceptible population to increase until the disease can reinvade. As long as a vaccine is not free, either monetarily or through true or even perceived side effects (Bauch and Earn, 2004), demand will be insufficient to pay for the vaccine at some point, leaving some people unvaccinated. If the disease is contagious, it could then begin spreading again among non-vaccinated individuals. Thus, it is impossible to eradicate a vaccine-preventable disease through voluntary vaccination if people act in their own self-interest (Geoffard and Philipson, 1997; May, 2000; Bauch *et al.*, 2003).

The idea of prevalence-dependence has been addressed in mathematical models (Liu *et al.*, 1986, 1987), in model fitting and parameter estimation (Gubbins and Gilligan, 1997a, 1997b), and in the modeling of HIV/AIDS (see e.g. Blower and McLean, 1994; Blower *et al.*, 2002; Blower *et al.*, 2003a; Blythe *et al.*, 1991; Brauer *et al.*, 1992; Hethcote *et al.*, 1991; Velasco-Hernandez and Hsieh, 1994). For example, Blythe *et al.* (1991) used an S-I model to show that susceptible individuals' behavior, represented by the contact rate and probability of infection, responds to perceptions of the overall prevalence of the disease.

Models of prevalence-dependent behavior also have significant impacts for vaccine policy formation. For instance, in an analysis of the hypothetical introduction of a vaccine that would protect against HIV, Blower and McLean (1994) found that individual levels of risk behaviors were a significant barrier to eliminating HIV. They showed that the prevalence of HIV could increase if risk behavior increased in the face of a mass vaccination campaign, even if the vaccine were highly efficacious. Other models have confirmed those results for HIV (Anderson and Hanson, 2005; Blower *et al.*, 2002; Blower *et al.*, 2003b; Bogard and Kuntz, 2002; Gray *et al.*, 2003; Hadeler and Castillo-Chavez, 1995; Smith and Blower, 2004; Stover *et al.*, 2002) and Auld (2003) speculates that this may have contributed to the decision not to release existing semi-efficacious vaccines.

Prevalence-dependent risk behavior or disinhibition has also been shown to have undesirable consequences for a program of expanding access to

[2] Kremer cautions, however, that at some point the risk becomes so great that individuals may become fatalistic, suggesting that there is a critical level that policy makers should be concerned about.

antiretroviral drugs. Blower *et al.* (2000) use a mathematical model to show how the widespread use of antiretroviral therapy (ART) could lead to the perverse result of an increase in disease prevalence. In their model, this therapy would not only reduce the death rate from HIV/AIDS, but, by reducing viral titres, it would also reduce the likelihood of transmission during a single sexual encounter. This favors more risky behavior, however, and they estimate that, as a result of introducing the therapy, a 10 per cent increase in risk behavior would lead to a net increase in the incidence of new cases.

Similar results were found by Hyman and Li (1997) in examining the effects of behavior change related to sexually transmitted diseases (STDs). They noted that once a certain level of prevalence has been reached, changes in behavior have little impact on an epidemic. Only at the initial stages of an epidemic, when prevalence is low, can a change in behavior – in this case, reductions in unprotected sexual contact – arrest the spread of an epidemic. This, they suggest, means that surveillance combined with educational campaigns may be able to prevent some epidemics before they become established, but behavior change after that point may have only a limited impact on the epidemic.

Although STDs are logical targets for examining the role of human behavior in a modeling framework, personal actions are important for other infectious diseases as well. Del Valle *et al.* (2005) used a mathematical model to examine behavioral changes induced by a smallpox outbreak. They demonstrate that the spread of the disease is highly sensitive to the rapidity with which people reduce their contact rate with others, and that even small reductions in the contact rate can significantly affect the spread of the disease. One would expect similar results for diseases like influenza or severe acute respiratory syndrome (SARS).

Epidemiologists have long recognized that community behavioral patterns are necessary elements in planning for disease control, but these elements have rarely made their way into mathematical models. One of the most studied elements has been community education, which has great potential for reducing disease. However, despite the emphasis placed on community interventions in practice, there is no clear evidence for their efficacy (Ghebreyesus *et al.*, 1996; Cline and Hewlett, 1996; Cairncross *et al.*, 1996; Gubler and Clark, 1996; Espinoza-Gómez *et al.*, 2002). One reason may be that individual and community behavior does not always respond to information in a way that seems intuitively obvious to policy makers. Community interventions may have weaker than anticipated or even perverse effects if behavioral responses critical to the spread of a disease are ignored. For example, individuals respond not only to a vaccine, but also to the anticipated release of a vaccine. In a model for timing the publicity surrounding the release of a vaccine, Auld (2003) suggests that if individuals believe that the probability of getting infected in the future is lower because of the anticipated release of a vaccine, they will likely reduce their risky behavior prior to the release of the vaccine, because they anticipate the disease will be less prevalent in the future. However, if the release of a vaccine is unanticipated, and individuals assume that the disease will be worse in the future, they will not reduce their risky behavior

now. In short, the more pessimistic individuals are about the future, the more risky their current behavior will be, and that can change the long-run prevalence of the disease.

Detection and diagnosis

Detection and diagnosis are important strategies for containing and treating infectious diseases because they enable identification of target populations of infected individuals and susceptibles. The availability and deployment of diagnostic methods may, however, have counterintuitive effects on the transmission of infection. Consider HIV/AIDS. If testing were costless, accurate, and immediate, uninfected patients might not engage in risky sex without prior testing. But testing costs money, is potentially inaccurate, and carries the risk of social stigma. In addition, the lag between infection and a positive test, aversion to learning that one is infected, and even legal sanctions for knowingly infecting someone with HIV, lower the demand for testing and complicate the dynamics of infection. Failure to account for these factors in epidemiological models may invalidate analyses predicting the effectiveness of strategies to manage the spread of disease. For example, mandatory testing is seen as a way of reducing the spread of HIV/AIDS. Under universal mandatory testing, an individual would be more likely to demand a partner's status before engaging in sexual contact, since the partner's refusal would suggest that it was positive. Instituting such a testing regime would be costly, and possibly face significant legal hurdles, but non-universal mandatory testing may actually increase the spread of disease (Philipson and Posner, 1993). With non-universal mandatory testing, a person at high-risk who would not have undergone testing voluntarily, and then tests negative may consider the good result a license to continue high-risk behavior and subsequently become infected.[3]

The benefits of targeting a primary disease for control must be considered in relation to all other causes of morbidity and mortality in a population. If the risks from other causes are high, the value of a life saved through primary control is lower because of morbidity and mortality from other causes. On the other hand, the control of a primary agent also changes an individual's incentives to invest in complementary risk-reducing interventions. Without considering complementarities, the benefits of controlling the primary disease are often underestimated because analysis overestimates mortality from alternative causes. For example, by lowering a child's risk of mortality from a childhood disease, such as measles or malaria, parents are more likely to invest in complementary health inputs, such as nutrition, that further reduce their risk of morbidity and mortality (Dow *et al.*, 1999).

[3] Epidemiologists have suggested this may be an issue (McCombie, 1986) but are inconclusive on the direction of effect (see Wenger *et al.*, 1991). In some studies counseling and testing seem to have some risk-reduction effect; however, the reductions are not large and there are no studies of its long-term effectiveness in preventing infection.

4. Externalities

An externality occurs when an individual's action, such as taking an antibiotic or spraying to control mosquitoes, results in costs or benefits to others that are not taken into consideration by the individual. For example, an individual who is treated with antibiotics creates a positive externality in that the action limits the spread of the disease. However, the treatment generates a negative externality as well: the increased likelihood of the development of resistant bacteria. Similarly, spraying DDT to control mosquitoes in and around a house has a positive externality for neighbors, since it reduces the number of infected mosquitoes in the area, but it may also damage the environment or people's health – a negative externality.

Externalities themselves are implicit in mathematical models of disease but the behavior of agents in the context of externalities is often ignored. Pathogen transmission is influenced by individual-level decisions, which may take into account what is in the individual's own self interests but not necessarily that of society.

Drug treatment increases the rate that infected hosts recover, thus reducing the prevalence of a disease and the risk of infecting susceptible hosts in the population. In conventional epidemiological disease models, this amplifies the benefits of treating a disease, especially if the pathogen can be locally eliminated. In this case the risk is reduced to zero until the pathogen is reintroduced. Since patients ignore the benefits of their treatment on others they may not go for treatment as much as is socially desirable, which may result in an increased spread of disease. In that case a government intervention to increase the use of antimicrobials may be necessary to protect society as a whole.

Externalities are the focus of a study by Miguel and Kremer (2004) that looked at the benefits of deworming across a wide area. They found that deworming an entire school reduced absenteeism at the school by more than a quarter, which would be expected. However, they also found that treatment significantly reduced the absenteeism rate of students in non-participating schools. The positive externality gained by treatment was so significant that they estimated it to be one of the most cost-effective health interventions for less developed countries. However, individuals were not willing to pay for their own deworming since they did not necessarily value the benefit of their actions on others. While externalities abound in infectious diseases, the kind of randomized evaluations carried out by Kremer and Miguel may not always be feasible. Mathematical models can play a useful role here in assessing the extent of disease externalities to determine the appropriate level of policy response.

On the other hand, as noted, treatment also has a negative externality: the risk that resistance will evolve in the pathogen population. For example, resistance to penicillin appeared soon after it was introduced into clinical practice in the 1940s. And resistance to new antibiotics has emerged on a regular basis since (Chambers, 2001; Murray, 2000), though patterns of emergence are unpredictable across pathogen species. Resistance is important because resistant bacterial infections are harder to treat and cause increased morbidity, mortality, and costs for patients and hospitals (Carmeli *et al.*, 2002; Cosgrove *et al.*, 2003; Cosgrove *et al.*, 2005; Engemann

et al., 2003; Gould, 2006; Martone and Nichols, 2001; McHugh and Riley, 2004; Rubin *et al.*, 1999; Song *et al.*, 2003; Stosor *et al.*, 1998). The significant threat of antibiotic resistance in the United States – which the CIA has labeled a national security risk (CIA, 2000) – as well as in the world (WHO, 2001), suggests that governments may need to act to reduce antibiotic use either directly, by controlling the quantity used, or by imposing taxes on antibiotics, or indirectly, by encouraging greater infection control. While ethical issues make limiting the supply of antibiotics problematic, better infection control would mean fewer infections and less use of antibiotics, thus lowering the risk of resistance. Infection control would also prevent the spread of both sensitive and resistant pathogens, and thus also serves to lower the risk of resistance. Hospitals, for instance, can control the spread of resistance by enforcing measures, such as hand washing and isolating carriers, that limit opportunities for disease transmission (Boyce and Pittet, 2002).

So what should governments do? Do they promote the use of antimicrobials to limit the spread of disease or restrict their use to control resistance? The answer is difficult because measuring the net benefit of antimicrobials is difficult. Governments ideally want to protect both the interests of individuals with infections and the global need for sustainable antimicrobial use. Striking the right balance is difficult in part because it is important to optimize over time. Diseases that spread have consequences now, but the emergence of resistance will more likely affect future generations. Therefore, policy decisions have to weigh current costs and benefits against those occurring for future generations (Smith, 2003). Choosing between containment of disease and containment of resistance is an area where disease models can help determine the optimal solution.

Modeling institutional behavior

Externalities apply not just to individuals but also to institutions, such as hospitals, schools, day-care centers, and prisons, which play a focal role in the spread of infectious diseases (Block, 2004; Freudenberg, 2001). Despite their obvious importance in disease transmission and the consequent costs to society as a whole, these institutions usually make their own decisions regarding infection control policy (Glaser and Greifinger, 1993; Roberts *et al.*, 2000b). Hospitals, for instance, often allocate little funding to infection-control units because of a failure of budgetary mechanisms, the decentralization of budgets and responsibility (Croxson *et al.*, 2003), or uncertainty over the benefits of infection control (Graves, 2004). The result is that infections must be treated, often by antibiotics, and a large portion of the resultant costs is passed on to insurance companies or patients and their families (whose costs include excess suffering or death), with the rest being absorbed by the hospital (Graves, 2001). Hospitals, at least, are in the health care business. Other institutions, such as prisons and schools, may choose to take no action because the costs are borne entirely by others.

Many pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and other resistant and non-resistant strains of bacteria, are typically spread both within a hospital by nurses, residents, and doctors and between hospitals by patients. Infection control is expensive, involving isolation and barrier nursing

of infected patients and frequent changes of hospital clothing. Hospitals also share patients. Frequently, a person colonized in one facility may be responsible for introducing drug-resistant pathogens in another facility. Since no single hospital (especially given short-term financial pressures) will see the full benefits of an infection-control program, each hospital may prefer to free ride on the infection control investments of other hospitals. The result is an overall higher level of antibiotic resistance. Modeling shows that the selfishly 'optimal' level of hospital infection control that any hospital would undertake is lower the greater the number of hospitals that share a catchment area (Smith *et al.*, 2005). In fact, it may be in the interests of the hospital to spend less and free-ride on the efforts of other hospitals.

Certain features of the solution to this coordination problem are of interest both to economists and epidemiologists. First, the noncooperative outcome among hospitals that share patients comes as no surprise to economists but offers a novel explanation for why infections may be more prevalent in areas with several institutions that share patients.[4] Second, the optimal investment in infection control by each hospital is sharply discontinous with respect to what other institutions do. A hospital may choose to go from a large infection-control program to a very small one in response to a steady inflow of infected patients. Such sharp nonlinearities are unusual in purely economic models that ignore disease dynamics.

5. Global disease commons

Increasingly, epidemiological models are addressing the large-scale spread of disease at national and international levels (Ferguson *et al.*, 2003; Keeling *et al.*, 2001). Here, too, strategic behavior on the part of governments and other policy makers will affect the spread of disease. In the United States for example, it is the states, not the federal government, that are ultimately responsible for making health policy decisions. Elsewhere in the world, countries are free to make their own health decisions. Since every state or country chooses its own self-interested level of protection from infectious diseases, without some sort of strategic cooperation across borders, diseases will continue to spread. Globalization, with frequent air travel and increased movement of goods, only increases the risks of rapid and extensive spread of infectious diseases.

Epidemiological modeling has attempted to address these issues by focusing on network structures and allowance for small-world connections (Keeling, 2005; Moore and Newman, 2000). This may provide a framework for addressing the coordination problems inherent in dealing with worldwide open-access commons, such as the efficacy of antibiotics and other antimicrobials or disease eradication. These types of 'goods' are in many ways an extension of externalities that economists have labeled global commons.

Global commons, by definition, are things that cannot be restricted to just one country – climate, for example. Climate change is a worldwide phenomenon: no one country can stop climate change alone, and the

[4] For instance, prevalence of MRSA has been, and continues to be, higher in relatively large urban medical centers than in smaller (<200 beds) community hospitals (Chambers, 2001).

actions of one or a few countries can undermine the actions of all others. A similar argument holds for the efficacy of antimicrobials as a global commons. If a pathogen becomes resistant to an antimicrobial due to overuse in one country, this resistant form is likely to spread throughout the world. For example, chloroquine was the main drug for treating malaria for several decades, but its efficacy has been waning sharply in recent years as the frequency of chloroquine resistance has increased (Snow *et al.*, 2001; Trape, 2001). While the mechanisms that engender resistance are not fully understood, it is believed that resistance to chloroquine has arisen only two to four times over the last 70 years (Payne, 1987; Wootton *et al.*, 2002), yet many countries, both in Africa and other regions of the world, have high rates of chloroquine-resistant parasites because chloroquine resistance has spread from just a few points of origin across national borders and among continents to become a global problem.

To help explain the causes of resistance and suggest ways to deal with the global commons problem of resistance, economists, as noted previously, have proposed that it may be appropriate to think of anti-infectives, such as antibiotics or antimalarials, as a natural resource, similar to fisheries, forests, and oil and minerals, areas that economics has a lot of experience in (Laxminarayan and Brown, 2001). Even though the mechanisms leading to resistance are not completely understood, there is a consensus that resistance does arise and a simple SIS (susceptible–infected–susceptible) model is capable of elucidating many of the issues of its spread. The question then becomes one of tradeoffs between current consumption and the risk of future decreased effectiveness. The answers are neither easy nor reassuring, but economics has a lot to say about how people value things at different points in time. For instance, in an examination of the impact of consumer choice on the spread of resistance to anti-malarial drugs both exogenously and endogenously, three recent studies find strong support for the subsidization of Artemisinin combination therapies as a means to reduce the spread of resistance (Laxminarayan, 2004; Laxminarayan *et al.*, 2005, 2006b). Ignoring the impact of consumer choice would have possibly led to different policy options, which is significant in light of the enormous sums of money needed to subsidize these combination therapies.

Similar to resistance evolution, the eradication of a disease is also a global commons, since the local elimination of a disease from one country can be undone by the failure to eliminate the disease in all countries. Again malaria provides an example. The disease was locally eliminated from many countries following an intensive worldwide spraying operation funded by international donors. But a backlash to the use of DDT resulted in the cancellation of the program before the parasite had been eradicated. This, combined with the reduced efficacy of chloroquine has resulted in the return of the disease to regions where it had been well controlled or even eliminated (Roberts *et al.*, 2000a).

An obvious benefit of eradicating a disease is that there are no more infections, but an additional benefit rarely discussed by epidemiologists is the avoidance of the costs of all future control efforts. These savings are generally many times larger than the cost of the eradication of infections. For example, the United States would save approximately $230 million

annually if polio were eradicated (US Congress, 1998), and estimates for the world suggest the savings may be as high as $1.5 billion annually (Aylward *et al.*, 2000; Bart *et al.*, 1996). Eradicating polio worldwide would allow resources that are currently spent on vaccinations to be put to more productive uses. The idea of a global disease commons is powerful. Indeed, the global eradication of smallpox is a candidate for the most cost-effective program ever, measured in terms of lives saved from smallpox as well as savings from the costs of smallpox vaccination (Barrett, 2004).

If the benefits of disease eradication are so large, why is there difficulty in attaining these targets? Economic game theory offers some insight. Assuming four identical countries, four possibilities present themselves: (1) no country eliminates the disease because it is too difficult; (2) no country eliminates the disease because of choice, regardless of what other countries do; (3) every country chooses to eliminate the disease, regardless of what others do; and (4) every country eliminates the disease if and only if every other country also eliminates the disease (Barrett, 2003). The coordination game (number 4) is most interesting in the context of the global economy, because institutions such as the United Nations and the World Health Organization can coordinate efforts across different countries, even though neither agency has real enforcement power (Barrett, 2004). The analysis of this problem lends itself to a combined consideration of game theory and metapopulation dynamics – the latter addressing the level of control that should be achieved to promote extinction and hence global eradication. A simple example of a metapopulation model to analyze invasion and extinction of plague in rat and human populations is given by Keeling and Gilligan (2000).

In cases where it would be in the global interest to eradicate a disease, but individual countries face different elimination choices, it may be in the interest of wealthier nations to pay for the elimination of diseases in poorer countries in order to achieve eradication. Barrett (2004) concludes that usually the benefits to high-income countries from eradication will be so great that they should be willing to finance elimination in low-income countries. Yet, even though this may make sense analytically, countries often choose not to help eradicate a disease because they don't think others are paying their share (the cooperation game) or the benefits are so diffuse that it is hard to marshal support. Global institutions can play a role here by helping coordinate efforts, and promoting understanding of the benefits of eradication. There is clearly scope for addressing this issue using a combination of epidemiological models to characterize the underlying spatial and temporal dynamics at the local (country) and global scales, together with economic modeling to identify dynamic costs and benefits.

Addressing these differences is important, because, in the real world, all countries are not the same. However, they can be easily accommodated into game theory and metapopulation models. Differential levels of infection and access to resources for control also focuses attention on the north–south divide. Most developed countries can choose to eliminate a disease, assuming it is possible to do so, and arguably will do so, if the benefits outweigh the costs. For many developing countries, however, the necessary

institutions do not exist or do not function well enough to eliminate a disease, even if the benefits outweigh the costs, which they may not. For example, countries experiencing polio outbreaks often have small public health budgets as well as competing priorities. One might ask, should polio vaccination or cholera control take precedence in refugee camps? Cholera is a major cause of morbidity and mortality in refugee camps, where case fatality rates can range between 3 and 30 per cent (Toole and Waldman, 1997), yet cholera poses a limited risk (and thus a limited benefit) to rich countries. Rich countries do, however, subsidize polio vaccinations. The huge influx in dollars from rich countries can often distort local public health priorities.

Unfortunately, there is no one-size-fits-all solution for any disease. Smallpox, for example, was a deadly disease; the feasibility and the clear economic desirability of eradicating it was demonstrated, yet efforts almost failed for lack of money (Henderson, 1999). Polio, on the other hand, despite a well-financed global effort (Aylward *et al.*, 2000), has not been eradicated yet and can still cause outbreaks in developed countries (Diamond and York, 2005). The interplay between national health agencies and the international system is a perfect example of where economic theories about strategic behavior and clear epidemiological models can be combined to advance understanding and inform public policy. Because infectious diseases do not respect political borders and political and economic incentives are both extremely heterogeneous, it is important to try to define the role that governments and institutions can play in coordinating a response, in financing and educating eradication efforts, and in combating other problems, such as surveillance and resistance, that may require different and potentially more difficult solutions.

6. Conclusions and further research

Much of this paper has focused on what economics can add to improve the quality of infectious disease models and public policy responses to disease. In conclusion, here we offer three observations to improve the quality of economic analysis of infectious disease.

First, economists need to pay attention to the specifics of a particular disease and to the specific effects of control. Although there are general insights that economists could draw from the most rudimentary disease models, the applicability of these insights is likely to be limited when constrained by the realities of a particular disease and its epidemiology. For example, Gersovitz and Hammer (2003) explore the externalities generated from prevention and therapy in an attempt to move beyond vaccination policies, but policy generalization is difficult when every disease has its own mode of transmission. More specific recommendations that arise from economic models that incorporate details of a particular disease are more likely to be useful in setting disease policy (Laxminarayan, 2004; Laxminarayan *et al.*, 2005).

Second, there is great potential for thinking about informational asymmetries in the context of disease. How people respond to the threat of disease depends on their perception of risk, which is influenced by public and private information. Public information can be published data on the

prevalence of a disease, which in turn can be disseminated widely by the media. Individuals combine this information with their own private sources of information and beliefs to assess their likely exposure to disease, which in turn determines their strategy for prevention. For example, individuals who think they live in an area of low prevalence of West Nile virus are relatively less likely to protect themselves from mosquitoes. However, the quality of information on local prevalence of West Nile virus may be biased, either because few physicians know enough about the disease to report it or because information about the risk of the disease may not be available to ordinary citizens.

Similarly, individuals may overprotect, which can have additional consequences on the spread of disease, as in the case of a 1994 outbreak of plague in a state in India. The government's announcement of the disease caused many people to flee the state in an effort to escape the disease, potentially carrying it to other parts of the country (Ramalingaswami, 2001). Much more research is needed to understand how provision of information influences individual risk perception and how this influences actions that shape the evolution of epidemics.

Third, there is clearly a need to incorporate behavioral choices into mathematical models of the spread of disease. This is crucial if we want to improve the accuracy of predictions of the course and cost of an epidemic and develop appropriate policies. Economics has much experience in thinking about how people respond to risk, either by greater risk taking in other areas of their life (a substitution response) or by decreasing risk elsewhere (disease complementarities). A unified framework for thinking about these responses to risk could be usefully combined with infectious disease models for a better understanding of how diseases and humans interact.

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