Chapter 19

MODELING OF ANTIBIOTIC RESISTANCE IN THE ICU — U.S. SLANT

Marc Lipsitch, D.Phil.
Department of Epidemiology
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115
lipsitch@epinet.harvard.edu

Carl T. Bergstrom, Ph.D.
Department of Biology
Emory University
1510 Clifton Road
Atlanta, GA 30322
cbergst@emory.edu

Abstract Mathematical models are valuable tools with which to predict and explain the epidemiology of nosocomial infection. As such, modeling will play a crucial role in the effort to control the growing threat posed in hospitals by antibiotic-resistant bacteria. In this chapter, we illustrate the utility of the model-based approach, using a simple mathematical model of colonization and infection by antibiotic-sensitive and resistant bacteria in a hospital setting. The model explains a number of otherwise counterintuitive observations regarding the spread of nosocomial resistance: (1) non-specific infection control measures such as hand-washing will disproportionately reduce the prevalence of resistant bacteria within the hospital; (2) resistance-control interventions should generate reductions in resistance much more rapidly in hospitals than in communities as a whole; (3) treatment with one antibiotic may be an individual risk factor for acquisition of resistance to another antibiotic, even in the absence of genetically linked resistance mechanisms.

1. WHY MATHEMATICAL MODELS?

Mathematical models have made substantial contributions to our understanding of the within-host population dynamics of microorganisms and the epidemiological dynamics of infections (1, 2). Such models underlie our present understanding of phenomena as diverse as the multi-year cycles of measles incidence and their changes following vaccination (1), the dynamic state of viral replication during the "latent" period in HIV infection (3, 4), and the maintenance of immune memory (5, 6). Recently, such models have been used — with particularly promising results — to evaluate the relationship between antimicrobial use and antimicrobial resistance, both at the level of individual patients and at the hospital or community level (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17).

In the context of those infections that are acquired in a hospital or ICU, models will be valuable for answering three questions of particular interest:

- How fast will resistance to a particular antibiotic rise in response to increased use? Will it appear rapidly in a large fraction of treated hosts, as in monotherapy of tuberculosis (18); will it take several decades but then spread rapidly in some institutions, as with vancomycin resistance in enterococci (19); or will it appear rapidly but remain rare, except in immunocompromised patients, as in the case of acyclovir resistance in herpes simplex viruses (20, 21)?

- How fast is resistance expected to decline if use of an antibiotic is reduced (8, 9, 13, 22, 23)? Will dramatic changes be seen within weeks to months (24, 25, 26, 27, 28), or will it take several years to see a substantial change (9, 29)?

- When an individual receives antimicrobial treatment, what is the effect on resistance in the bacteria in that individual, in other individuals in the same hospital or ward, and in other individuals in the community at large (30)? What are the relationships among these different effects, and which ones are most important to measure?

Despite the success of mathematical models in beginning to address these and other questions about antimicrobial resistance, the use of population biological modeling in this domain is sometimes greeted with a degree of skepticism. The concerns are essentially twofold.

Some critics suggest that mathematical models are too complicated to be useful, that models are merely complicated (and often confusing) restatements of results already well-known through clinical experience. Such a skeptic might wryly point out, for example, that it does not take a rocket scientist, let alone a mathematical epidemiologist, to realize that increasing the use of an antibiotic is likely to increase the level of resistance to that antibiotic. There is indeed a valid

point here. It is certainly appropriate to ask, “What do I know, or understand, after seeing the results of this mathematical model, that I did not know, or did not understand, before seeing them?" The answer to this question determines — to a large extent — the value of the model to users, such as clinicians, epidemiologists, and public health planners. However, it is essential to realize that even when the models do not yield results that are qualitatively surprising, quantitative description of epidemiological phenomena is crucial to the design and evaluation of interventions to control resistance. To evaluate whether an intervention might be worthwhile (or whether one has been successful), it is necessary to know how large an effect the intervention should have and how quickly its benefits should accrue. Indeed, the work described in this chapter will illustrate the utility of models for these purposes.

A second set of skeptics argue essentially the opposite, asserting that mathematical models are too simple to be useful in the complex world of hospital epidemiology. This group points out that the transmission dynamics of antimicrobial-resistant organisms, especially in the hospital, are extremely complicated, and that mathematical models are far too idealized to capture this complexity; therefore, it is asserted, the models cannot hope to be of any help. Such skeptics might go on to argue that since the goal is to reduce the effect of resistance on morbidity and mortality, the important thing is to figure out what works in the real world.

Certainly, we do not dispute the complexities inherent to the biology and epidemiology of resistance. Rather, we acknowledge a number of particularly thorny complexities associated with hospital epidemiology. These include

- The tremendous diversity in the genetic bases, biochemical properties, drug specificities, and fitness consequences of resistance mechanisms.

- Difficulties in pinpointing the routes and causes of transmission of sensitive and resistant organisms when a carrier state that typically precedes disease, as is the case in most nosocomial infections. This process is further complicated by the roles of health care workers as vectors of transmission (8) and the manner in which the hospital environment serves as a reservoir of microorganisms.

- Ignorance about the role of the normal flora in modulating an individual’s susceptibility to colonization by bacteria from the environment or to overgrowth of endogenous bacteria (31, 32).

- The probable importance of rare, “random," and unpredictable events that can have major consequences for the epidemiology of resistance. These events occur on a global scale, as when resistance to a particular drug first appears in a species of clinical significance, and they are then

repeated locally, in a particular community or hospital, when a resistant organism or a new set of resistance genes is introduced from outside.

Despite these complexities, carefully constructed models that incorporate key features of hospital epidemiology can provide useful answers to questions about the relationships among antibiotic use, infection control, and antibiotic resistance. The models will indeed be simplifications, and an important step in the modeling process is to check whether the predictions of the models are robust, or whether they are artifacts introduced by the simplifications themselves. Because of these complexities, we are not enthusiastic about the abilities of models to “fit" precisely and quantitatively the time course of particular epidemics of resistant pathogens. Rather, we think that models can be valuable for the study of antimicrobial resistance in general, and in the ICU in particular, in three ways:

- by making testable, quantitative predictions about the epidemiology of a particular pathogen that were not apparent to intuition alone,
- by suggesting explanations for epidemiological phenomena that have been observed but whose mechanisms were not understood, and
- by aiding in the design and justification of standards for judging the success of interventions that are intended to control resistance in a specific context.

In this chapter, we describe a simple mathematical model of the transmission dynamics of antibiotic-resistant and -sensitive bacteria in a hospital or a unit of a hospital. We hope that this model and its predictions will exemplify all three of these uses for models.

2. A MODEL FOR HOSPITAL-ACQUIRED INFECTIONS

Several fundamental differences — with important epidemiological consequences — distinguish hospital-acquired infections from their community-acquired counterparts. First, for most of the important nosocomial pathogens, asymptomatic colonization of the skin, upper respiratory tract, or gut by the bacteria normally precedes infection (33). As a consequence, transmission of the bacteria typically proceeds from carrier to carrier, rather than from infected case to infected case. Second, a hospital or intensive care unit has highly fluid human and microbial populations, unlike most other communities in which resistance is studied. The average patient in many hospital units stays only about a week (34, 26, 30) and therefore the hospital population turns over rapidly, bringing in bacteria from outside and discharging them, with the patients, back

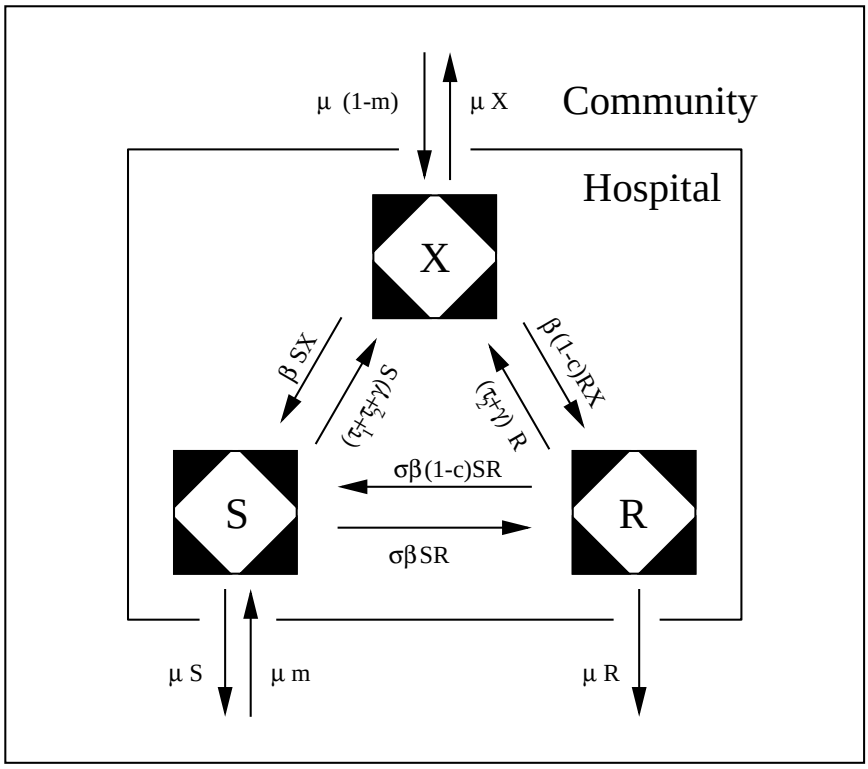

Figure 19.1 A simple compartment model of bacterial tranmission dynamics in a hospital setting. Patients may be uncolonized (X), colonized with sensitive bacteria (S), or colonized with bacteria resistant to drug 1 (R). Patients enter (and leave) the hospital at rate μ per day; of the newly-admitted patients, a fraction m are colonized with sensitive bacteria and $1 - m$ are uncolonized. Colonization of the uncolonized patients occurs by mass action with transmission rate parameter β; resistant bacteria suffer a proportional reduction in transmission rate of c. Superinfection — the infection and conversion of already-colonized individuals — occurs at a rate σ relative to infection of uncolonized individuals. Patients are treated with drug 1 and drug 2 at rates τ_1 and τ_2 per day, respectively, and patients spontaneously clear bacterial colonization at a rate γ per day. The model is fully specified by three ordinary differential equations: $dS/dt = m\mu + \beta SX - (\tau_1 + \tau_2 + \gamma + \mu)S + \sigma\beta cSR$; $dR/dt = \beta(1-c)RX - (\tau_2 + \gamma + \mu)R - \sigma\beta cSR$; $dX/dt = (1-m)\mu + (\tau_1 + \tau_2 + \gamma)S + (\tau_2 + \gamma)R - \beta SX - \beta(1-c)RX - \mu X$.

into the community. This flow of patients and bacteria between community and hospital can be seen in Figure 19.1.

The model in Figure 19.1 is designed to reflect the transmission dynamics of a single bacterial species, which is transmitted among individuals within the hospital (or ICU). Within the hospital, the model considers three populations of patients: those not carrying the bacterial species of interest (hereafter, the

bacteria), those carrying bacteria sensitive to a particular drug ("drug 1"), and those carrying bacteria resistant to drug 1. The number of individuals in each group is given by X, S, and R respectively. Patients may enter the hospital in any of these categories. For mathematical simplicity, we will describe the model for the special case in which patients carrying resistant bacteria enter only very rarely; most newly admitted patients are either uncolonized by the bacteria or are carrying sensitive bacteria. We describe elsewhere (13) how the model changes if large numbers of patients enter the hospital carrying resistant bacteria.

Once in the hospital, patients may be treated with either of two drugs. If they are treated with drug 1, patients carrying sensitive bacteria will be cleared (S patients will be converted into X patients). By contrast, patients treated with a second, unrelated drug (drug 2) will be cleared of their bacteria, regardless of which kind of bacteria they carry; we assume for this basic model that all bacteria are sensitive to drug 2. Patients not carrying either kind of bacteria can be colonized, either by sensitive or resistant bacteria, at rates proportional to the current prevalence of that kind of bacteria. Patients already carrying sensitive bacteria may be colonized with resistant bacteria, and vice versa, but this "super-colonization" process occurs at a rate lower than the colonization of uncolonized patients. Patients may spontaneously clear carriage of bacteria of either sort, at a low rate. Patients from each category leave the hospital at a fixed rate.

The mathematical details of this model have been given elsewhere (13). Rather than recapitulate them here, we instead summarize some of the clinically important predictions of the model, and compare these predictions with data from the literature on nosocomial infections and resistance.

3. MODEL PREDICTIONS, EMPIRICAL DATA, AND CLINICAL IMPLICATIONS

The model defines the conditions under which resistant bacteria can persist in the hospital, and conversely defines the conditions under which endemic resistant bacteria can be eradicated. Endemic transmission of resistant bacteria can persist in the hospital if the transmission rate of bacteria in the hospital is sufficiently high, if use of drug 1 is sufficiently common, if use of drug 2 is sufficiently rare, and if the average length of stay is sufficiently long. Figure 19.2 shows how these parameters trade off with one another. If within-hospital transmission rates β are high (Fig. 19.2a), then resistant bacteria can persist despite relatively rates τ_1 of drug 1 use. If within-hospital transmission rates are reduced, then a higher level of drug 1 use is required to maintain endemic transmission of bacteria resistant to drug 1. As the rate τ_2 of use of drugs for which resistance is not present increases (Fig. 19.2b), higher rates

of transmission β (or higher rates of drug 1 use) are required for endemic persistence of resistant bacteria. In hospitals (or units) where the average length of stay $1/\mu$ is longer, endemic transmission of resistant bacteria is more easily maintained (Fig. 19.2c).

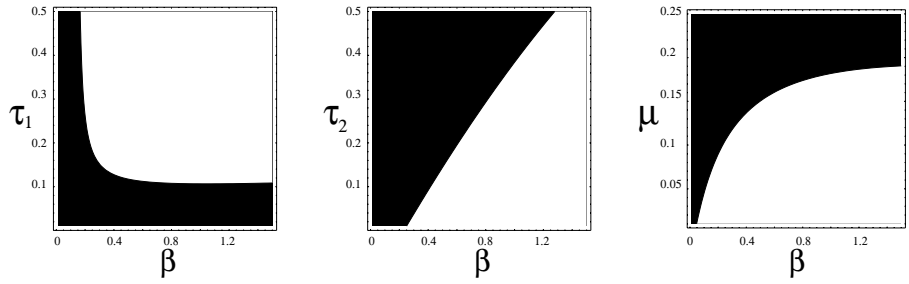

Figure 19.2 Parameters for which resistant bacteria can persist (white) and cannot persist (black) in the hospital (see text). Parameters (except when varied on x or y axes): $c = 0.05$, $\gamma = 1/30$, $m = 0.75$, $\tau_1 = 0.2$, $\tau_2 = 0$, $\mu = 0.1$, $\sigma = 0.25$.

These predictions have several implications for the control of resistance in a hospital. As Figure 19.2 demonstrates, different interventions — reduction in the use of the drug to which resistance is observed, increased use of other antimicrobials, and infection control measures aimed at generally reducing within-hospital cross-colonization of patients — can achieve the goal of reducing or eliminating resistant bacteria. In some cases two partially successful measures can in concert result in elimination of endemic transmission, although neither would have sufficed alone.

Even without the model, it is clear that one way to approach this goal is to reduce use of the antibiotic to which the bacteria are resistant; this intuition is confirmed by the model. Less clear is how the use of other antimicrobial agents, to which bacteria are not resistant, affects the transmission of bacteria resistant to a particular drug (drug 1 in our model). Clinical studies and clinical practice give conflicting evidence on this point. On one hand, many studies show that antimicrobial use in general is a risk factor for colonization or infection with bacteria resistant to a particular drug (35, 36, 37, 38, 39, 40, 41) (the model's predictions for such studies are discussed below). Presumably following this logic, one response to problems of resistance has been to curtail use of all antibiotics in a hospital or unit (26, 42). On the other hand, the use of antimicrobial prophylaxis to reduce resistance (34), or the implementation of antimicrobial cycling programs (43, 44) both rely on the intuition that the use of some drugs, for which resistance is not observed, can help control the level of resistance to other drugs, for which resistance is a problem.

The model's prediction supports the latter intuition, that increased use of one antimicrobial agent (drug 2) can help reduce the prevalence of resistance to another drug (drug 1). A key caveat to this prediction is that the bacteria resistant to drug 1 are not cross-resistant to drug 2. Thus, the prediction would not be appropriate for closely related drugs sharing the same resistance mechanism, or for drugs for which resistance genes are linked on a plasmid.

The model predicts that infection control measures such as hand-washing and barrier precautions, which are directed nonspecifically at reducing transmission of all bacteria, will disproportionately help to reduce the prevalence of resistant bacteria. Figure 19.3 shows the predicted prevalence of colonization with sensitive and resistant bacteria at equilibrium in the model, as a function of the rate of within-hospital transmission β. For a wide range of transmission rates β (given that resistance can persist in an endemic state), decreases in the transmission rates decrease the equilibrium prevalence of resistance more than they affect the equilibrium prevalence of sensitive bacteria. Notice that this prediction provides a further rationale for the importance of infection control in the hospital as a measure for reducing antimicrobial resistance.

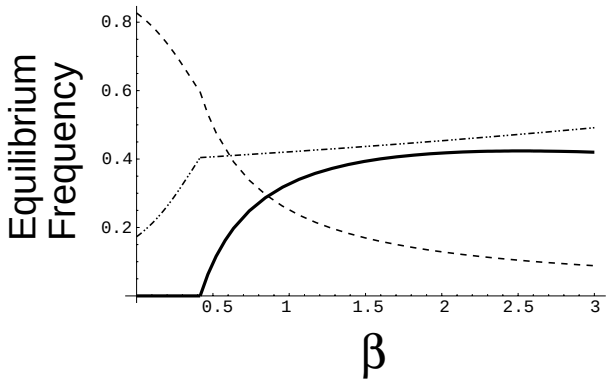

Figure 19.3 Equilibrium frequency of uncolonized individuals (dashed line), individuals colonized with sensitive bacteria (dash-dotted line), and individuals colonized with resistant bacteria (solid line). When resistant bacteria are endemic, decreases in transmission rate typically reduce disproportionately the frequency of resistance. Parameters are as in Figure 19.2, except $\tau_2 = 0.1$.

Though counterintuitive at first glance, this observation can be explained from the structure of the model shown in Figure 19.1. Patients enter the hospital either carrying sensitive bacteria or none, but only very rarely carrying resistant bacteria. Thus, resistant bacteria depend for their survival solely on transmission within the hospital, while sensitive bacteria are maintained both by transmission in the hospital and by "immigration" with newly admitted patients. Reductions in transmission therefore do disproportionate harm to resistant bacteria.

The model predicts that successful interventions will reduce resistance in a very short time, within weeks or a few months. Figure 19.4 shows the change in the prevalence of colonization with resistant bacteria, starting from an equi-

librium level, following various interventions. As the figure demonstrates, different interventions will have different effects, but in each case noticeable change is apparent within a very short time period. Such rapid changes are observed for very wide ranges of parameters, as long as the average stay of a patient in the hospital is assumed to be days or weeks.

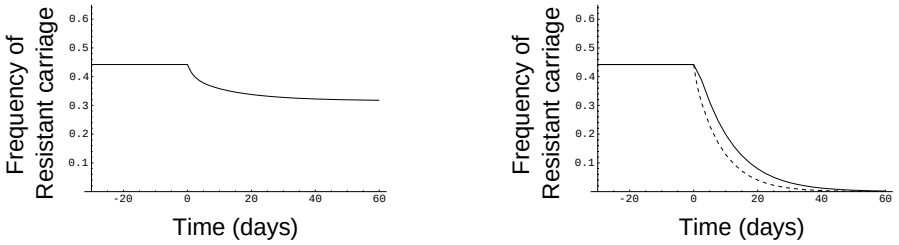

Figure 19.4 Response to resistance control interventions: frequency of resistance carriage after (a) reduction of transmission rate by 50%; (b) cessation of drug 1 use with (dashed line) and without (solid line) replacement by use of drug 2. Parameters are as in Figure 19.2.

The reason for the rapid changes in prevalence of resistant and sensitive bacteria is the rapid "flow" of patients through the hospital, and the fact that some of the newly entering patients bring sensitive bacteria with them. Thanks to this constant influx of sensitive bacteria, which compete with resistants to colonize patients, resistant bacteria cannot persist in the hospital for long if conditions are unfavorable for their transmission. Interestingly, in contrast to other models of the transmission dynamics of antimicrobial resistant bacteria, this process does not depend on a difference in Darwinian fitness (transmissibility, ability to colonize, or ability to persist within a patient) between sensitive and resistant bacteria. In a hospital (under our assumptions), the entry of patients already carrying sensitive bacteria will replenish the sensitive population rapidly, allowing them to out-compete resistant bacteria whenever conditions are no longer favorable for the resistant strains (due to reduced transmission, reduced use of the drug to which they are resistant, etc.).

This prediction is consistent with the observed consequences of interventions designed to reduce resistance in hospitals. Many of these interventions result in substantial changes in the prevalence of resistance within a very short time (25, 26, 27, 28). The prediction is specific to nosocomial infections, because it depends on the entry into the system of individuals (from outside) who carry sensitive bacteria. Thus, it would not be expected to hold for most community-acquired infections, and indeed it does not. In the rare cases where interventions intended to limit resistance in community-acquired pathogens have been reported, their success has occurred on a time scale of years (9, 29). The model thus suggests that when interventions to reduce resistance in hospitals do not produce rapid results, it is appropriate to seek a specific explanation for the

failure: perhaps, a longer average duration of stay than in most hospitals, or the existence of a reservoir — an environmental source or a long-term colonized patient or health care worker — which could be slowing the "wash-out" of resistant bacteria.

The model predicts that, measured at the individual level, use of one antibiotic (drug 2) will be a risk factor for colonization with bacteria resistant to another antibiotic (drug 1). This result is paradoxical because, as we have just seen, the use of drug 2 can help to reduce the prevalence of bacteria resistant to drug 1 in the hospital as a whole. Thus, there is a positive association between drug 2 use and drug 1 resistance for individuals, but a negative association between drug 2 use and the total prevalence of resistance to drug 1 (at the population level). These relationships are shown in Figure 19.5.

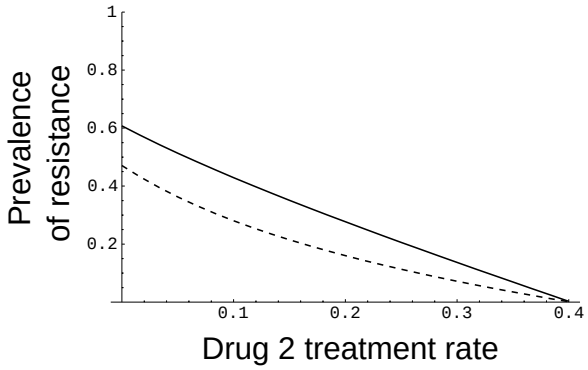

Figure 19.5 Equilibrium frequency of drug 1 resistance carriage in individuals treated with drug 2 (solid line), and untreated with drug 2 (dashed line). Increasing drug 2 usage decreases the overall frequency of resistance in the hospital, but individuals treated with drug 2 are always more likely to be infected by bacteria resistant to drug 1. For numerical tractability, an example with no superinfection is shown (parameter values are $c = 0.05$, $\gamma = 1/30$, $m = 0.75$, $\tau_1 = 0.2$, $\tau_2 = 0$, $\mu = 0.1$, $\sigma = 0$). Qualitatively similar results obtain when superinfection is present.

Like some of the previous predictions, this opposition between individual risk and population-wide effects is a consequence of the entry of individuals already carrying drug-sensitive bacteria into the hospital, and is therefore not expected to appear in community-acquired infections. We see this result in hospitals because treatment with drug 2 has two opposing effects on bacteria resistant to drug 1: (a) If a patient already carries sensitive bacteria, drug 2 clears bacterial carriage and increases the chance that the individual will be colonized by bacteria resistant to drug 1, which are circulating in the hospital; (b) if an individual already carries bacteria resistant to drug 1, drug 2 clears their carriage of these resistant bacteria. At the individual level, the effect (a) is more powerful, while at the level of the population, effect (b) is stronger.

This prediction of the model is consistent with published studies of antimicrobial use and resistance in hospitals. Such studies often find an association at the individual level between prior use of one antibiotic and infection or colonization with bacteria resistant to another drug (45, 38, 41). Sometimes, this association has a trivial explanation; for example, the same gene, or two genes located on the same plasmid, might determine resistance to both drugs. However, in several cases no such explanation is available; for example, quinolones (for which resistance is chromosomal) have been detected as a risk factor for carriage of enterobacteria carrying plasmid-mediated cephalosporin resistance (45, 41).

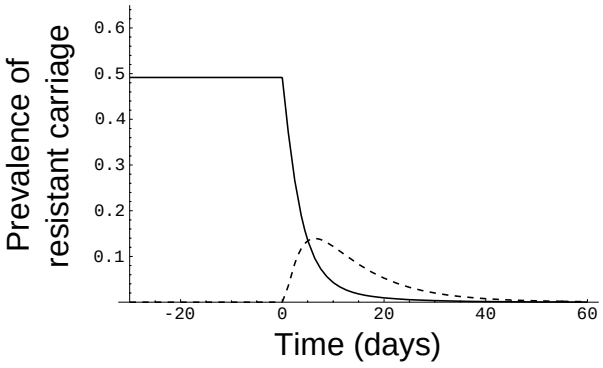

Figure 19.6 Dynamics of resistance after switching from using drug 1 exclusively to using drug 2 exclusively, at time 0. The frequency of resistance declines rapidly as a consequence, even though individuals treated with drug 2 (dashed line) are temporarily at greater risk of acquiring bacteria resistant to drug 1 than are individuals who remain untreated with drug 2 (solid line). Parameters are as in Figure 19.5.

In highlighting the opposition between individual and population-level consequences of intervention, the model shows that information about individual risk factors cannot be extrapolated to predict the effects of interventions at a population level (46). This distinction means that it is crucial to measure the right quantities when assessing the effects of interventions. For example, if a hospital chose to switch its formulary from empiric therapy with one drug (for which resistance had become a problem) to therapy with another drug (for which resistance was rare) (43), the model predicts that the use of the new drug would help to bring down resistance to the first, but that as resistance to the first declines, patients treated with the second drug would be at increased risk of carrying resistance to the first. If only individual risk factors were measured in this hospital, one might erroneously conclude that the new drug was responsible for maintaining resistance to the old drug, whereas in fact it was contributing to the decline of that resistance. Such a situation is illustrated in Figure 19.6.

4. CONCLUSIONS, CAVEATS, AND FUTURE DIRECTIONS

In this chapter, we have illustrated the way in which a simple mathematical model can be applied to the problem of antibiotic resistance in hospitals and ICUs. Of course, several caveats must be noted. While the model suggests that in the short term, resistance to one drug can be controlled by the use of a second drug, it would be a mistake to treat this prediction as a prescription, without considering several additional factors. First, the model assumes that there is no resistance to drug 2; when resistance to drug 2 is present in the population as well, more complicated models (and perhaps consideration of drug-cycling strategies) will be required. Second, even in the absence of resistance to drug 2, the use of this drug will presumably select for the generation of resistance to it and therefore broad use may be undesirable. Third, use of drug 2 in order to control resistance to drug 1 may accelerate the evolution of multiply-resistant strains of bacteria, which could in turn pose a far more grave threat than either singly-resistant strain.

Despite these limitations, our results illustrate all three of the general applications of modeling that were mentioned in the introduction. First, the model makes testable predictions that were not intuitively obvious. For example, the model predicts that in hospitals, resistance-control interventions should should take effect rapidly, within a matter of weeks to months and that if change does not occur on this time scale, specific explanations (e.g. environmental reservoirs) should be sought. Second, the model allows us to explain mechanistically a series of puzzling observations about hospital-acquired infections. By taking into account the constant flow of patients between hospital and community and the commensal nature of many bacterial species responsible for nosocomial infections (including the fact that individuals entering the hospital may already be colonized), the model explains why (1) reducing transmission disproportionately affects the prevalence of resistant bacteria; (2) microbial populations in hospitals can respond to interventions within a very short time span compared to community acquired infections; (3) treatment with one antibiotic can be a risk factor for bacteria that are resistant to another antibiotic. Third, and perhaps most importantly, the model provides insight for designing standards by which to judge the success of interventions. In particular, our analysis illustrates the way in which static epidemiologic measures of association (individual risk factors) can be misleading predictors of the effects of intervention.

References

[1] R. M. Anderson and R. M. May. *Infectious Diseases of Humans: Dynamics and Control*. Oxford University Press, Oxford, 1991.

[2] B. R. Levin, M. Lipsitch, and S. Bonhoeffer. Population biology, evolution, and infectious disease: Convergence and synthesis. *Science*, 283(5403):806–9, 1999.

[3] D. D. Ho, A. U. Neumann, A. S. Perelson, W. Chen, J. M. Leonard, and M. Markowitz. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*, 373:123–126, 1995.

[4] X. Wei, S. K. Ghosh, M. E. Taylor, V. A. Johnson, E. A. Emini, P. Deutsch, J. D. Lifson, S. Bonhoeffer, M. A. Nowak, and B. H. Hahn. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*, 373(6510):117–22, 1995.

[5] C. A. Michie, A. McLean, C. Alcock, and P. C. Beverley. Lifespan of human lymphocyte subsets defined by CD45 isoforms. *Nature*, 360(6401):264–5, 1992.

[6] M. K. Slifka, R. Antia, J. K. Whitmire, and R. Ahmed. Humoral immunity due to long-lived plasma cells. *Immunity*, 8:363–372, 1998.

[7] D. J. Austin and R. M. Anderson. Transmission dynamics of epidemic methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci in england and wales. *J Infect Dis*, 179(4):883–91, 1999.

[8] D. J. Austin, M. J. Bonten, R. A. Weinstein, S. Slaughter, and R. M. Anderson. Vancomycin-resistant enterococci in intensive-care hospital settings: Transmission dynamics, persistence, and the impact of infection control programs. *Proc Nat Acad Sci U S A*, 96(12):6908–13, 1999.

[9] D. J. Austin, K. G. Kristinsson, and R. M. Anderson. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci U S A*, 96(3):1152–6, 1999.

[10] S. M. Blower, T. C. Porco, and G. Darby. Predicting and preventing the emergence of antiviral drug resistance in HSV-2. *Nature Medicine*, 4:673–678, 1998.

[11] S. M. Blower, P. M. Small, and P. C. Hopewell. Control strategies for tuberculosis epidemics: New models for old problems. *Science*, 273(5274):497–500, 1996.

[12] T. B. Kepler and A. S. Perelson. Drug concentration heterogeneity facilitates the evolution of drug resistance. *Proc Nat Acad Sci U S A*, 95(20):11514–9, 1998.

[13] M. Lipsitch, C. T. Bergstrom, and B. R. Levin. Antibiotic resistance in hospitals: Paradoxes and prescriptions. Submitted, 1999.

[14] M. Lipsitch and B. R. Levin. The population dynamics of antimicrobial chemotherapy. *Antimicrobial Agents and Chemotherapy*, 41(2):363–73, 1997.

[15] M. Lipsitch and B. R. Levin. Population dynamics of tuberculosis treatment: Mathematical models of the roles of non-compliance and bacterial heterogeneity in the evolution of drug resistance. *International Journal of Tuberculosis and Lung Disease*, 2(3):187–99, 1998.

[16] R. M. Ribeiro and S. Bonhoeffer. A stochastic model for primary HIV infection: optimal timing of therapy. *AIDS*, 13(3):351–7, 1999.

[17] N. I. Stilianakis, A. S. Perelson, and F. G. Hayden. Emergence of drug resistance during an influenza epidemic: Insights from a mathematical model. *J Infect Dis*, 177(4):863–73, 1998.

[18] N. Rist. Nature and development of resistance of tubercle bacilli to chemotheraputic agents. In V. C. Barry, editor, *Chemotherapy of Tuberculosis*, pages 192–227. Butterworths, London, 1964.

[19] R. Leclerq, E. Derlot, J. Duval, and P. Courvalin. Plasmid-mediated resistance to vancomycin and teicoplanin in *enterococcus faecium*. *New England Journal of Medicine*, 319:157–161, 1988.

[20] J. Christophers, J. Clayton, J. Craske, R. Ward, P. Collins, M. Trowbridge, and G. Darby. Survey of resistance of herpes simplex virus to acyclovir in northwest England. *Antimicrobial Agents and Chemotherapy*, 42:868–72, 1998.

[21] L. Corey. Herpes simplex virus infections during the decade since the licensure of acyclovir. *Journal of Medical Virology*, Suppl. 1:7–12, 1993.

[22] S. J. Schrag, V. Perrot, and B. R. Levin. Adaptation to the fitness costs of antibiotic resistance in Escherichia coli. *Proceedings of the Royal Society of London, Ser. B*, 264:1287–1291, 1997.

[23] F. M. Stewart, R. Antia, B. R. Levin, M. Lipsitch, and J. E. Mittler. The population genetics of antibiotic resistance. II: Analytic theory for sustained populations of bacteria in a community of hosts. *Theor Popul Biol*, 53(2):152–65, 1998.

[24] J. M. Boyce, M. Landry, T. R. Deetz, and H. L. DuPont. Epidemiologic studies of an outbreak of nosocomial methicillin-resistant Staphylococcus aureus infections. *Infect Control*, 2(2):110–6, 1981.

[25] M. Cosseron-Zerbib, A. M. Roque Afonso, T. Naas, P. Durand, L. Meyer, Y. Costa, N. el Helali, G. Huault, and P. Nordmann. A control programme for MRSA (methicillin-resistant Staphylococcus aureus) containment in a paediatric intensive care unit: Evaluation and impact on infections caused by other micro-organisms. *J Hosp Infect*, 40(3):225–35, 1998.

[26] L. M. Dunkle, S. H. Naqvi, R. McCallum, and J. P. Lofgren. Eradication of epidemic methicillin-gentamicin-resistant Staphylococcus aureus in an intensive care nursery. *Am J Med*, 70(2):455–8, 1981.

[27] J. A. Franco, D. V. Eitzman, and H. Baer. Antibiotic usage and microbial resistance in an intensive care nursery. *Am J Dis Child*, 126(3):318–21, 1973.

[28] H. A. Lilly and E. J. Lowbury. Antibiotic resistance of Staphylococcus aureus in a burns unit after stopping routine prophylaxis with erythromycin. *J Antimicrob Chemother*, 4(6):545–50, 1978.

[29] H. Seppala, T. Klaukka, J. Vuopio-Varkila, A. Muotiala, H. Helenius, K. Lager, and P. Huovinen. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N Engl J Med*, 337(7):441–6, 1997.

[30] A. M. Garber. A discrete-time model of the acquisition of antibiotic-resistant infections in hospitalized patients. *Biometrics*, 45(3):797–816, 1989.

[31] R. Freter, E. Stauffer, D. Cleven, L. V. Holdeman, and W. E. Moore. Continuous-flow cultures as in vitro models of the ecology of large intestinal flora. *Infect Immun*, 39(2):666–75, 1983.

[32] D. van der Waaij. *Antibiotic choice: The importance of colonisation resistance*. Research Studies Press, Chichester, 1983.

[33] M. J. Bonten and R. A. Weinstein. The role of colonization in the pathogenesis of nosocomial infections. *Infection Control and Hospital Epidemiology*, 17:193–200, 1996.

[34] C. Brun-Buisson, P. Legrand, A. Rauss, C. Richard, F. Montravers, M. Besbes, J. L. Meakins, C. J. Soussy, and F. Lemaire. Intestinal decontamination for control of nosocomial multiresistant gram-negative bacilli. Study of an outbreak in an intensive care unit. *Ann Intern Med*, 110(11):873–81, 1989.

[35] R. Gaynes and D. Monnet. The contribution of antibiotic use on the frequency of antibiotic resistance in hospitals. *Ciba Found Symp*, 207:47–56, 1997.

[36] J. C. Lucet, S. Chevret, D. Decre, D. Vanjak, A. Macrez, J. P. Bedos, M. Wolff, and B. Regnier. Outbreak of multiply resistant enterobacteriaceae in an intensive care unit: Epidemiology and risk factors for acquisition. *Clin Infect Dis*, 22(3):430–6, 1996.

[37] J. E. McGowan, Jr. Is antimicrobial resistance in hospital microorganisms related to antibiotic use? *Bull N Y Acad Med*, 63(3):253–68, 1987.

[38] J. G. Morris, Jr., D. K. Shay, J. N. Hebden, R. J. McCarter Jr., B. E. Perdue, W. Jarvis, J. A. Johnson, T. C. Dowling, L. B. Polish, and R. S. Schwalbe. Enterococci resistant to multiple antimicrobial agents, including vancomycin. Establishment of endemicity in a university medical center. *Ann Intern Med*, 123(4):250–9, 1995.

[39] G. G. Rao. Risk factors for the spread of antibiotic-resistant bacteria. *Drugs*, 55(3):323–30, 1998.

[40] G. G. Rao, F. Ojo, and D. Kolokithas. Vancomycin-resistant gram-positive cocci: Risk factors for faecal carriage. *J Hosp Infect*, 35(1):63–9, 1997.

[41] J. Wiener, J. P. Quinn, P. A. Bradford, R. V. Goering, C. Nathan, K. Bush, and R. A. Weinstein. Multiple antibiotic-resistant Klebsiella and Escherichia coli in nursing homes. *JAMA*, 281(6):517–23, 1999.

[42] D. J. Price and J. D. Sleigh. Control of infection due to Klebsiella aerogenes in a neurosurgical unit by withdrawal of all antibiotics. *Lancet*, 2(7685):1213–5, 1970.

[43] M. H. Kollef, J. Vlasnik, L. Sharpless, C. Pasque, D. Murphy, and V. Fraser. Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, 156(4 Pt 1):1040–8, 1997.

[44] J.E. McGowan, Jr. Minimizing antimicrobial resistance in hospital bacteria: Can switching or cycling drugs help? *Infect Control*, 7:573–576, 1986.

[45] C. De Champs, D. Rouby, D. Guelon, J. Sirot, D. Sirot, D. Beytout, and J. M. Gourgand. A case-control study of an outbreak of infections caused by Klebsiella pneumoniae strains producing CTX-1 (TEM-3) beta-lactamase. *J Hosp Infect*, 18(1):5–13, 1991.

[46] J. S. Koopman and I. M. Longini, Jr. The ecological effects of individual exposures and nonlinear disease dynamics in populations. *Am J Public Health*, 84(5):836–42, 1994.