

# Models for the spread of resistant pathogens

B.R. Levin

## ABSTRACT

I consider three mathematical models of the epidemiology of antibiotic treatment and the evolution of resistance. All of these models explore the relationship between the volume of antibiotic use and the frequency and rate of ascent (or descent) of resistance. The first model is in the population genetics tradition and assumes that in the absence of treatment the frequency of resistance wanes at a rate proportional to the fitness costs associated with resistance, but precipitously ascends to high frequencies in treated patients. The second two models are in the compartment, or SIR, model tradition of infectious disease epidemiology. The first of these considers the relationship between resistance and rates of antibiotic treatment in open communities. The second explores the factors contributing to the frequency of resistance in the closed settings of hospitals and nursing homes. While I give some consideration to the epidemiological and medical implications of the results of the analysis of the properties of these models, for the most part the models are the message. I end with a harangue about the utility of simple mathematics for these considerations and a plea to obtain realistic estimates of the parameters of these models and test the validity of the predictions generated from the analysis of these models.

## INTRODUCTION

The use and misuse of antibiotics and other antimicrobial agents has resulted in the evolution and ever-increasing frequency of pathogenic microbes that are resistant to them. Because of resistance, drugs that had been successfully used to prevent or treat infections with bacteria, viruses and protozoa are no longer effective. From a medical and public health perspective, there is no way of seeing a positive side to this rise in resistance. For mathematical modellers, on the other hand, drug resistance offers us not only another career opportunity but one that enables us to make a useful contribution to the society that pays our way. Mathematical models can be used to elucidate the magnitude of the contribution of the different factors and processes responsible for the rise (and descent) of resistant microbes and interpret the results of empirical studies of the epidemiology of drug resistance. They can also be used to design and evaluate drug-use regimes to control the ascent of resistant microbes in infected hosts, in open communities and in the confines of hospitals and nursing homes.

In this report, I provide an egotistical (focusing mostly on our own work) overview of some of the mathematical models that have been used to address questions of the relationship between the rate and pattern of antibiotic use and the frequency and rate of change in the frequency of antibiotic

resistant bacteria. While I use the words 'antibiotic' and 'bacteria' and like them best, with simple modifications these models (as well as those developed by others) could be applied to other antimicrobial agents and other micro-parasites. To make this consideration more readable for a general audience, I present these models and the results of the analysis of their properties in an intuitive (and hopefully intelligible) way. The models I consider here and the details of the analysis of their properties have already been published in the cited articles. In describing the results of the analysis of the properties of these models, I briefly consider their implications for the future antibiotic resistance problem. I conclude with a short and hopefully not too preachy discussion of the utility of simple mathematical models for these considerations and the need to obtain realistic, independent estimates of their parameters and test the validity of the predictions generated from the analysis of the properties of these models.

## POPULATION GENETIC MODELS

One approach to exploring the relationship between antibiotic use and antibiotic resistance is to use the gene frequency models similar to those employed by population geneticists,

e.g. as detailed in.<sup>1</sup> In the case of bacteria one can assume with some justification that the populations are haploid and there is no recombination, so that there are two phenotypes (genotypes) to consider: one that is susceptible to the antibiotic under consideration and one that is resistant, S and R. Antibiotics enter these models in the determination of the relative fitness of the sensitive and resistant genotypes.

In a recent article, Daren Austin and colleagues<sup>2</sup> used a model of the population genetic ilk to explore the relationship between the rate of increase in the frequency of resistance and antibiotic use. They assumed that the relative fitness of the resistant bacteria increases with the volume of antibiotics used and declines as the frequency of resistance increases. The latter being based on the reasonable assumption that as antibiotic resistance becomes more common, the rate of use of that antibiotic will decline. In their model, the rate of ascent of resistance was proportional to the volume of antibiotics, and there can be a stable polymorphic equilibrium with sensitive and resistant bacteria present in the community.

A few years ago we used a somewhat, but not much, more mechanistic population genetics model to ascertain the relationship between the frequency of antibiotic use and the level of resistance.<sup>3,4</sup> In these models we considered a population of hosts some of whom were under antibiotic treatment and some not. In the simpler version of this model<sup>3</sup>, we assumed that in the absence of antibiotic treatment, the frequency of the resistant genotype would wane at a rate proportional to the fitness cost associated with resistance. We used the standard population genetics selection coefficient,  $s$  ( $0 < s < 1$ ) per generation as our measure of the cost of resistance. We assumed that every time a host was treated, the frequency of resistant bacteria in that host would ascend to unity, no matter what that frequency was before treatment. We further assumed that bacteria were excreted into a common environment at a rate  $f$  and picked up from that environment at a rate  $g$  per generation.

In this model there is a stable polymorphic equilibrium when the rate of loss of resistance due to the fitness costs in untreated hosts and the environment is exactly compensated for by the ascent of resistance in the hosts under treatment. By numerical (computer) simulation, we calculated the relationship between the equilibrium frequency of resistance, the selection coefficient,  $s$  and the annual rate at which people were treated with the selecting antibiotic.

The results of this analysis were not optimistic. For example, with one treatment a year, and a fitness cost of resistance of  $s=0.01$  and environmental exchange rates of  $f=0.05$  and  $g=0.005$ , the anticipated frequency of resistance at

equilibrium is  $\sim 0.53$ . With one treatment every second year, this equilibrium frequency is  $\sim 0.32$ . If the cost of resistance is greater, the equilibrium frequency will be lower. For example if resistant bacteria grow at a rate 2% less than sensitive,  $s=0.02$ , for one treatment per year and one treatment every second year the equilibrium frequencies of resistance would be  $\sim 0.33$  and  $\sim 0.18$  respectively.

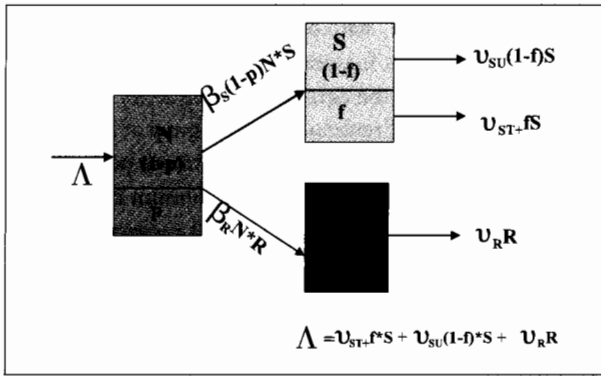
## EPIDEMIOLOGICAL MODELS

### A model for the epidemiology of antibiotic treatment and prophylaxis in open communities

An alternative approach to modelling the relationship between antibiotic use and resistance is in the compartment or SIR tradition of the models employed by infectious disease epidemiologists.<sup>5</sup> In these models, hosts are in different states with respect to the infection, i.e. uninfected, and infected with bacteria that are susceptible to treatment with an antibiotic. Uninfected hosts are converted into infected hosts at a rate that is proportional to their density (or in some cases like sexually-transmitted pathogens, their relative frequency) and that of infected hosts. Infected hosts change state through clearance of the infection, or removal from the population (death?) due to the infection or other causes.

In figure 1 I present the minimalist compartment model of the epidemiology of resistance used in.<sup>6</sup> Hosts are in three states: uninfected, infected with drug-sensitive microbes, and infected with drug-resistant microbes, with densities and designations,  $N$ ,  $S$  and  $R$ , respectively. Transmission is direct, and uninfected hosts can be infected with drug-sensitive or drug-resistant bacteria at rates proportional to their respective densities and rate constants of transmission,  $\beta_S$  and  $\beta_R$  respectively for the drug-sensitive and resistant bacteria. A fraction  $p$  of the uninfected host population is under prophylaxis with the antibiotic and can only be infected with resistant bacteria. Infected hosts are 'spontaneously' cleared of the bacteria at rates  $\nu_{SU}$  and  $\nu_R$  respectively. A fraction  $f$  of the susceptible host population is treated with an antibiotic that accelerates the rate of clearance  $\nu_{ST}(\nu_{ST} > \nu_{SU})$ . Treatment of  $R$  hosts has no effect on the rate at which the infection is cleared. We assume that there is no mortality and that susceptible hosts enter at exactly the same rate at which infected hosts are removed, so at any given time the total population density remains constant.

The infection can become established and will be maintained as long as in a wholly-susceptible host population a single infected individual is able to transmit the infection to at least one uninfected host before being cleared of the infection or dying, i.e. the number of secondary infections



**Figure 1**  
*Simple compartment model for the epidemiology of drug treatment and resistance*

$N$  denotes density of uninfected hosts,  $S$  denotes density of hosts infected with drug-sensitive bacteria,  $R$  denotes density of hosts infected with drug-resistant bacteria;  $\beta_S$  and  $\beta_R$  denote transmission rate constants of susceptible and resistant infections respectively;  $\nu_{SU}$ ,  $\nu_{ST}$  and  $\nu_R$  denote daily rates of clearance of untreated susceptible infections, treated susceptible infections and resistant infections respectively;  $p$  denotes the fraction of the uninfected population under prophylaxis,  $f$  the fraction of the population of hosts infected with susceptible bacteria that are under treatment.

(the basic reproductive number)  $R_0 > 1$ . In this model, on average a host infected with susceptible and resistant bacteria would maintain the infections for  $1/[(1-f)\nu_{SU} + f\nu_{ST}]$  and  $1/\nu_R$  days respectively. And in wholly-susceptible populations of density  $N$ , over the course of that time they would transmit the infection to  $\beta_S(1-p)N$  and  $\beta_R N$  hosts. Thus the basic reproductive numbers of drug-sensitive and drug-resistant bacteria in this population would be

$$R_{oS} = \beta_S(1-p)N / [(1-f)\nu_{SU} + f\nu_{ST}]$$

and

$$R_{oR} = \beta_R N / \nu_R$$

If the basic reproductive number of the resistant microbes exceeds that of the drug-sensitive ones,  $R_{oR} > R_{oS}$ , they will become established and eventually replace the susceptible population. As this model is now written, there are no conditions under which both sensitive and resistant microbes could coexist. With some complications, this kind of model could be modified to allow for the stable coexistence of sensitive and resistant microbes, e.g. as detailed.<sup>7</sup>

As can be seen from the above equations, whether resistant microbes will ascend and replace sensitive ones depends on the relative rates of transmission,  $\beta_S$ ,  $\beta_R$  (the higher the better for resistance), the relative rates at which they are cleared,  $\nu_R$ ,  $\nu_{SU}$ ,  $\nu_{ST}$  (the lower the better for resistance),

the fraction of the population under prophylaxis,  $p$ , and the fraction of host with susceptible infections treated,  $f$  (the more the better for resistance). With a little algebra, from these  $R_0$  equations we can calculate the threshold level of treatment or prophylaxis needed for resistance to ascend. For example, if there is no prophylaxis,  $p=0$ , as long as  $R_{oR} > 1$ , the fraction of the population that would have to be treated for resistance to invade would be

$$f > [(\beta_S/\beta_R)\nu_R \nu_{SU}] / (\nu_{ST} \nu_{SU})$$

By inspection of this inequality we can see that if  $(\beta_S/\beta_R)\nu_R < \nu_{SU}$  and  $\nu_{ST} > \nu_{SU}$  resistance will invade and replace sensitive bacteria whether there is treatment or not. On the other hand, as we hope and expect  $(\beta_S/\beta_R)\nu_R > \nu_{SU}$  the fate of the resistant bacteria will depend on the magnitude of  $f$  ( $f > 0$ ). The level of treatment,  $f_T$ , for resistance to invade and replace susceptible ones, is going to be inversely related to the efficacy of treatment as measured by the rate of clearance of treated and untreated infections, the difference between  $\nu_{ST}$  and  $\nu_{SU}$  and the cost of resistance, as measured by the difference between  $(\beta_S/\beta_R)\nu_R$  and  $\nu_{SU}$ . For example, consider a situation where  $\beta_S = \beta_R$  and where in the absence of treatment a susceptible infection takes an average of 10 days to clear,  $\nu_{SU} = 1/10 = 0.1$ , a resistant infection takes somewhat less time for clearance  $\nu_R = 0.11$ , and a treated susceptible infection is cleared in two days  $\nu_{ST} = 0.5$ . Under these conditions, resistance will become established and eventually dominate as long as  $f$  remains above 0.025, or 2.5% of the infected hosts are treated. If treatment is less effective, and five days are required for clearance,  $\nu_{ST} = 0.2$ , the threshold level of treatment for resistance to invade would be  $f_T = 0.10$ . Stated another way, the more effective an antibiotic is, the lower the threshold level of treatment needed for resistance to ascend. A lower treatment threshold would also obtain if resistance engenders little cost as measured by the rate of clearance,  $\nu_R$  and the transmission coefficient  $\beta_R$ . A totally ineffective antibiotic poses no resistance risk.

vanaf hier geen cursief ingevoerd

The dynamics of the ascent and descent of resistance in this model can be explored from the differential equations for the changes in the densities of these different host states specified by this model.

$$\begin{aligned} dS/dt &= \Lambda - N(\beta_S(1-p)S - \beta_R R) \\ dS/dt &= S(\beta_S(1-p)N - (1-f)\nu_{SU} + f\nu_{ST}) \\ dR/dt &= R(\beta_R N - \nu_{SR}) \end{aligned}$$

For our numerical analysis of the properties of this model we let the total density of the population remain constant by letting the input of susceptible hosts be exactly equal to the rate at which infected hosts were cleared  $\Lambda = S(1-f)\nu_{SU} + Sf\nu_{ST} + R\nu_R$ .

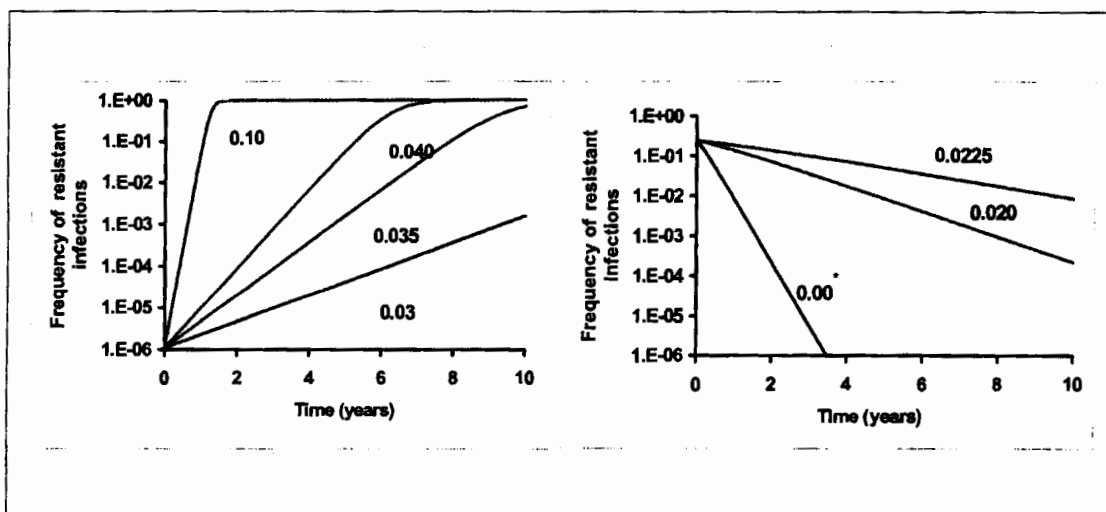


Figure 2  
Ascent and descent of resistance in an open community for different levels of treatment

Relative frequency of infections with resistant bacteria. Numerical solution to equations (1)-(3) above. In this simulation  $\beta_S = \beta_R = 10^{-6}$ ,  $\nu_{SU} = 0.10$ ,  $\nu_{SI} = 0.50$ ,  $\nu_R = 0.11$  (per day). With these parameters, in the absence of treatment, the anticipated equilibrium frequencies of uninfected hosts and those infected with susceptible bacteria,  $N$  and  $S$ , would be  $10^5$  and  $9 \times 10^5$ , respectively and the threshold level of antibiotic treatment above which selection will favour resistance if  $f_T = 0.025$ . The first part shows the ascent of resistance when antibiotic use exceeds the threshold; the second shows the decline in the frequency of resistance when the rate of antibiotic use is below the threshold. At the start of these simulations, the initial densities,  $N$ ,  $S$  and  $R$  were  $1.15 \times 10^5$ ,  $6.27 \times 10^5$  and  $2.19 \times 10^5$  respectively.

In figure 2, I consider the dynamics of the ascent and descent of resistance anticipated by this model. With the parameters in the legend to figure 2, the minimum densities of a wholly-susceptible host population necessary to maintain infections with susceptible and resistant bacteria are  $10^5$  and  $1.1 \times 10^5$  respectively. With these parameters and a total population of  $10^6$  hosts, in the absence of treatment and resistant bacteria, at equilibrium  $N=10^5$  and  $S=9 \times 10^5$ . In figure 2a we follow the changes in the relative frequency of resistant infections in a population initially at this  $N$ ,  $S$  equilibrium, into which a single host carrying resistant bacteria  $R=1$  is introduced and in which the level of antibiotic consumption exceeds the threshold,  $f > 0.025$ . In figure 2b we follow the decline in the frequency of resistance, following reductions in antibiotic use to levels below the threshold,  $f < 0.025$ . In these runs, the initial densities of the three different states were those obtained when  $f=0.04$  and the relative frequency of resistant strains was approximately 25%.

The implications of these simulation results are clear and roughly consistent with those observed in open communities:

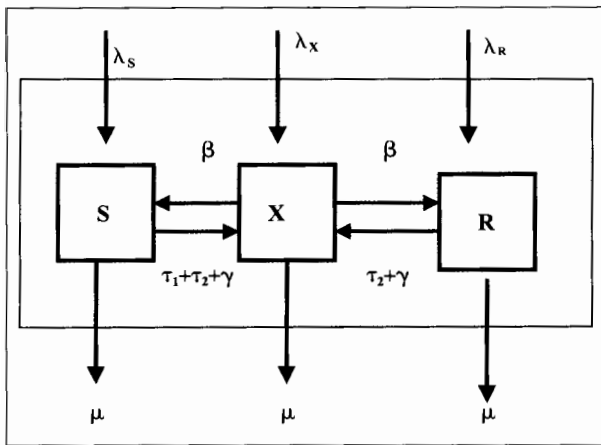
- 1) Relatively little antibiotic use can lead to the rapid ascent of resistance.
- 2) Once the frequency of resistance is at readily observable

levels, in the order of 1%, it won't be long before it will reach levels where it becomes problematic in the order of 25% or more.

- 3) The level of antibiotic use has to be reduced to well below the threshold,  $f_T$ , for the frequency of resistance to decline at a substantial rate.
- 4) The amount of time for the frequency of resistance to go from problematic to non-problematic levels following a successful campaign to reduce antibiotic use can be in the order of years or even decades.

#### A MODEL FOR THE EPIDEMIOLOGY OF ANTIBIOTIC TREATMENT AND RESISTANCE IN THE CLOSED SETTINGS OF HOSPITALS AND NURSING HOMES

Epidemiological models of antibiotic treatment and resistance can also be developed for specific situations or settings. One particularly important setting is that of hospitals and nursing homes. In these institutions the rate of antibiotic consumption is high, as is the susceptibility of patients to bacterial infection and its pathogenic effects. In figure 3, I present the minimalist model of the epidemiology of antibiotic treatment and resistance in hospitals we used.<sup>8</sup>



**Figure 3**  
*A compartment model for the epidemiology of anti-microbial chemotherapy and resistance in a hospital*

S, X and R respectively denote densities of patients carrying microbes sensitive to drugs 1 and 2, uninfected patients and patients carrying bacteria resistant to drug 1;  $\beta$  denotes rate constant of transmission;  $\tau_1$  and  $\tau_2$  denote rates of clearance of the infection per day due to treatment with drugs 1 and 2;  $\gamma$  denote rate of spontaneous clearance of the infection per day;  $\lambda_s$ ,  $\lambda_x$  and  $\lambda_r$ , respectively the number of patients infected with bacteria susceptible to both drugs, not infected and resistant to drug 1 entering the hospital each day. The rate of removal from the hospital,  $\mu$ , is set equal to the total rate of input, so the total number of patients in the hospital remains constant.

We assume that two antibiotics are employed in the hospital, 1 and 2. Patients are in three states with respect to infection with a nosocomial (hospital-acquired) pathogenic bacterium: S – carrying bacteria that are sensitive to both antibiotics, X – uninfected, and R – carrying bacteria resistant to the first of these antibiotics, where S, X and R are the densities as well as designations of patients in these states. Patients enter the hospital in one or another of these states at rates  $\lambda_s$  and  $\lambda_x$  and  $\lambda_r$  patients per day and collectively leave the hospital at the same rate as new patients enter,  $\mu$  patients per day. (The hospital is at steady state. All the beds are full and the administrators are very happy). Uninfected patients X can be infected with bacteria sensitive to both antibiotics at a rate equal to the product of their density, that of the S population and an infection rate constant,  $\beta$ . They can also be infected with resistant bacteria at a rate equal to the product of their density, S, and that of hosts with resistant infections, R. Infected hosts lose their bacteria spontaneously at a rate  $\gamma$  per day and enter the X population. Hosts in the S state can also be cleared of their infection by treatment with either antibiotic 1 or antibiotic 2 at rates  $\tau_1$  and  $\tau_2$  per patient per day. Patients with resistant infections, R, can be cleared of the infection spontaneously or by treatment with antibiotic 2.

The major qualitative results of the analysis of the properties of this model are straightforward and intuitively reasonable, at least they are by the second if not the first consideration:

- (1) The frequency of resistance to drug #1 is directly proportional to its rate of use  $\tau_1$ .  
Through more frequent use of drug 1, a greater number of hosts infected with susceptible bacteria, S, are converted into uninfected hosts, X, and thereby become subject to infection by hosts carrying resistant bacteria, R.
- (2) Drug-resistant and drug-sensitive bacteria can coexist in a stable state.

As long as  $\lambda_s > 0$ , there will always be patients with susceptible bacteria. Consequently, no matter how intense the selection for hosts carrying resistant bacteria may be, there is no way to eliminate all of those carrying bacteria sensitive to antibiotic 1.

- (3) The frequency of bacteria resistant to drug #1 can be reduced and these bacteria can be eliminated from the hospital by one or more of the following procedures:

- (i) Reducing the rate of use of drug: #1 reducing  $\tau_1$ .  
This occurs for the same reasons that increasing the use of that drug increases the frequency of hosts in the R state.

- (ii) Increasing the rate of use of drug #2: increasing  $\tau_2$ .  
By increasing the extent to which drug 2 is employed, the rate at which patients carrying resistant bacteria, R, are converted into the X state is increased and the R population has less time to infect them.

- (iii) Reducing the overall rate of transmission: reducing  $\beta$ .

By reducing the overall rate of transmission, fewer hosts in the X state become infected with resistant bacteria. And if no patients carrying resistant bacteria enter the hospital, whilst those carrying sensitive ones do, the frequency of resistance will disproportionately decline.

- (iv) Increasing the turnover rate of patients: increasing  $\lambda_s$ ,  $\lambda_x$  and  $\lambda_r$ .

By increasing the rate of turnover of infected hosts, S and R have less time to infect uninfected hosts before they become cleared of the infection. If there are no resistant bacteria entering the hospital (or fewer than susceptible) the effect of increasing the rate of turnover disproportionately reduces the frequency of resistant bacteria.

Among the more interesting – and I believe – important results of the analysis of the properties of this model can be seen the dynamics of the changes in the relative frequency of hosts infected with resistant bacteria. As one would anticipate, the rate of ascent of resistance is proportional to the amount of antibiotic use as measured by the rate at

which the antibiotic for which there is resistance clears the infection,  $\tau_1$  per day. Perhaps less anticipated is how rapidly resistance ascends. In the absence of any resistant bacteria entering the hospital but with high rates of antibiotic use, the frequency of resistance can ascend from a frequency  $10^{-3}$  to problematic levels  $>0.10$  within a month or two.

On the positive side, resistance will be eliminated from the hospital within weeks when 1) antibiotic use stops, 2) the rate of turnover of patients in the hospital is increased sufficiently, or 3) the rate of transmission is sufficiently reduced, 4) the frequency of resistance to antibiotic 1 can also be reduced at a reasonable rate to manageable levels by introducing a second antibiotic to which there is no resistance.

Ultimately, the successful control of resistance in a hospital is contingent on keeping patients bearing resistant bacteria from entering the unit in which resistance is being controlled. As can be seen in figure 4, even when antibiotic 1 is not used, if hosts carrying bacteria resistant to drug 1 enter the institution, resistance will persist.<sup>5</sup> Moreover, even without treatment, the frequency of resistance in the hospital can exceed that in the community. In this example, the frequency of patients with resistant bacteria is 25%, while the frequency in the hospital is even greater. The reason for this is that, because of transmission within the confines of the hospital, uninfected patients, X, get infected with resistant bacteria that are resident in the hospital.

## DISCUSSION AND CONCLUSION

### The utility of simple models

The models considered here are very simple analogues of the population genetics and epidemiology of antibiotic treatment and resistance in human communities and hospitals. We could talk extensively, if not wax eloquent, about how unrealistic they are and how they should be modified to make them more realistic and more precise. We could also argue for the utility, if not the mathematical aesthetics and elegance, of more complex, realistic and precise models. At this juncture, however, I believe precision is a luxury. The concern is not predicting the precise relationship between antibiotic use and resistance, but rather to identify the major factors determining this relationship and in a roughly quantitative way explore how they affect the direction and rate of change in the frequency of resistance and the general magnitude of these rates. Should we anticipate programmes calling for reductions in antibiotic use to lead to substantial declines in the frequencies of resistance? How much do we have

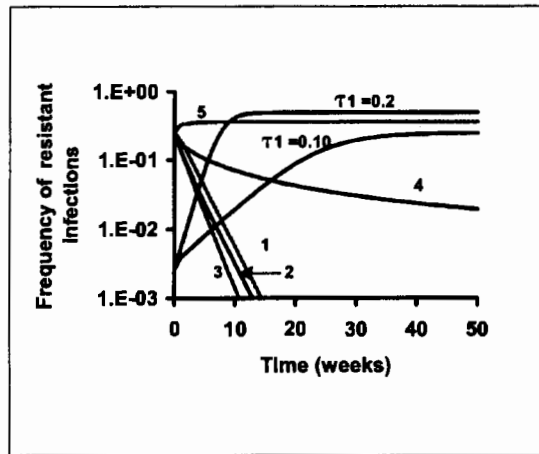


Figure 4  
Hospital model, simulation results

The frequency of resistant infections with different antibiotic use regimens. Standard parameters,  $\tau_1=0.10$ ,  $\tau_2=0.0$  per day,  $\beta=10^{-3}$ ,  $\lambda_3=\lambda_4=20$  per day,  $\lambda_5=0$ ,  $\gamma=0$  per day,  $N_{Tot}=400$ . With these standard parameters, at equilibrium  $S=200$ ,  $X=100$  and  $R=100$ . In the absence of antibiotic use,  $\tau_1=0$ ; with these standard parameters, at equilibrium  $X=S=200$  and  $R=0$ . 1 denotes terminating the use of antibiotic 1,  $\tau_1=0.0$ ; 2 denotes doubling the rate of turnover,  $\lambda_3=\lambda_4=40$  and  $\lambda_5=0$ ; 3 denotes reducing the rate of transmission to below the threshold  $\beta=10^{-3}$ ; 4 denotes introducing a second antibiotic for which there is no resistance,  $\tau_2=0.10$ ; 5 denotes terminating antibiotic use  $\tau_1=0.0$  but allowing patients carrying resistant bacteria to enter the hospital,  $\lambda_3=\lambda_4=15$  and  $\lambda_5=10$ .

to reduce antibiotic consumption to actually see the frequencies of resistance wane? How can we be sure a reduction in antibiotic consumption is the reason for observed declines in the frequency of resistance? Many other processes could account for the changes in a bacterial population, including declines in the frequency of resistance. If we can in fact reduce antibiotic use sufficiently, how long will it take before resistance wanes to non-problematic levels? Will it take months, years or decades? I suggest that, with realistic and independent estimates of the parameters of these simple models, these and other simple models could provide useful answers to these questions.<sup>2</sup>

### Parameter and test: a need for real work (as opposed to mathematical modelling)

While arguably in realistic ranges, the parameter values used in the numerical examples employed here are made up. They needn't have been. At least approximate values of these parameters could be estimated independently of the models in the laboratory or, even better, in natural populations. Using experimental populations of bacteria,

*in vitro* and *in vivo*, there have been a number of studies estimating the fitness costs associated with antibiotic resistance.<sup>9</sup> Unfortunately, from a human perspective, the results of these studies are not optimistic. Resistance often does not have a measurable cost, and even when it does, second-site, compensatory mutations can readily evolve to ameliorate those costs. The implication of this is that in the presence of continuous antibiotic use, the level of resistance may well remain high and the rate at which resistance wanes following sufficient reduction in antibiotic use may be quite low.

Unfortunately, from a scientific perspective, studies estimating the fitness costs of resistance have been restricted almost exclusively to the relative competitive performance of drug-susceptible and resistant bacteria. To my knowledge, there have been no independent estimates of the effect of resistance on the rates of transmission, the  $\beta_s$  in the compartment models or the rates at which infections are cleared, the parameters  $\nu_R$ ,  $\nu_{SU}$ ,  $\nu_{ST}$  in the model for resistance in open communities. These cost-of-resistance parameters are fundamental to predicting the future of resistance as well as designing programmes for antibiotic use to minimise the rate of ascent of resistance and maximise the rate of decline. For example, in their study of the factors responsible for the decline in resistance in Iceland, the model used by Austin and colleagues<sup>2</sup> makes a very specific prediction about the fitness costs of the resistant bacteria. By independently estimating these fitness parameters, it should be possible to directly ascertain whether the cause of that decline was in fact the reduction in antibiotic consumption.

The hospital model used here makes a number of optimistic predictions which, I believe, can be tested. They suggest a

variety of methods by which the frequency of infections with bacteria resistant to one or more antibiotics could be dramatically reduced even to the point of elimination (see the list on page 62). Most importantly, the effects of interventions directed at reducing resistance in these institutions should be seen in the order of months, well within the term of most research grants.

## REFERENCES

1. Crow JF, Kimura M. An introduction to Population Genetics Theory (1st edition). New York: Harper Row, 1971.
2. Austin D, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proceedings of the National Academy of Science of the United States of America* 1999;96:1152-6.
3. Levin BR, Lipsitch M, Perrot V, et al. The population genetics of antibiotic resistance. *Clin Infect Dis* 1997;24:S9-16.
4. Stewart FM, Antia R, Levin BR, Lipsitch M, Mittler JE. The population dynamics of antibiotic resistance II: analytical theory for sustained populations of bacteria in a population of hosts. *Theor Pop Biol* 1998;53:152-65.
5. Anderson RM, May RM. *Infectious Diseases of Humans: Dynamics and Control*. Oxford: University Press 1991, Oxford.
6. Levin BR. Mathematical models of the emergence and spread of antibiotic resistance. In: Andrementot CB-BA, McGowan JE (eds). *Antibiotic Therapy and the Control of Antibiotic Resistance in Hospitals*. 6th Maurice Rapin Colloquium. Paris: Elsevier, 1999. p. 39-51.
7. Massad E, Lundberg S, Yang HM. Modeling and simulating the evolution of resistance against antibiotics. *International Journal of Biomedical Computing* 1993;33:65-81.
8. Lipsitch M, Bergstrom CT, Levin BR. 2000 The epidemiology of antibiotic resistance in hospitals: Paradoxes and Prescriptions. *Proc Nat Acad Sci US* 2000;97:1938-43.
9. Andersson DA, Levin BR. The biological cost of antibiotic resistance. *Current Opinion in Microbiology* 1999;2:487-91.

## Discussion following lecture of B.R. Levin

*Verbrugh*: Perhaps we can discuss this in two parts. First, resistance and the community, because that, as you pointed out, is a different story from what we see in hospitals. Who wants to comment on resistance development in the community?

*R. de Boer*: I would buy the idea that the cost of resistance is low and hence the disappearance of resistance is slow.

But why then, if this is so, is the accumulation of resistance so slow? Why does it take decades to go to a 30% resistance, if resistant bacteria have virtually no costs of being resistant?

*Levin*: There is 30-40% vancomycin resistance in hospitals and 50% of *E. coli* is resistant to penicillins. So we are already up there. If we look at pneumococcus, we are seeing very high frequencies, particularly in countries like

Spain, where they use a lot of antibiotics. Over here they do not want to use a lot of antibiotics and so resistance is lower. As far as the cost of resistance is concerned, I think that we have other phenomena: we have clonal changes and other things that are changing frequencies of things. If I follow the *E. coli* in my flora after I have stopped using tetracycline, they waxed and waned and they went up and went down and without any change. The frequency never got very much less than 10<sup>-3</sup>, but it went up and down for reasons that have nothing to do with antibiotics, but it rather simply changes. In this case there is a wonderful example of the cost of resistance in HIV. One of our colleagues did a study where they had a protease-inhibitor that had markedly reduced fitness and then they let it evolve in culture. Two things happened. One is that the fitness increased and the other thing is that the level of resistance increased. So I think there are all sorts of other dynamics going on. In general, it is consistent with the idea of very intense selection and resistance really increasing. What I do not know is whether the countries that have used less antibiotics are lower on the scale, or are really at a different equilibrium. I do not think equilibrium is here yet.

*J. Vandenbroucke:* Thank you for your talk and also for coming back to the use of models. You made an aside that intrigued me, historically, and that is the remark about the children in the daycare centre having *E. coli* B resistant to streptomycin. Do you really think that it is a kind of remnant of the population imprint of the streptomycin use two or three decades ago?

*Levin:* I think that most of the resistance to streptomycin we saw was plasmid-borne. We see very little chromosomal resistance. So a lot of it is associated linkage selection and dates from decades ago. We pick up chloramphenicol resistance also. The other thing is that in the United States, I do not know about The Netherlands, we use streptomycin on our fruit trees, because we do not want blemishes. So it is not only therapeutic use of streptomycin that may cause this selection, it is also agricultural use. But I suspect that most of it is associated linkage selection.

*Leufkens:* What is the average number of days for hospital stay in your hospital?

*Levin:* I actually do not know. I know there is a great deal of pressure to reduce that for economic reasons. So I know it is declining in the USA.

*Leufkens:* It is declining in most countries, at least in the Western world. With that in the background, do you think it still would make sense to make a distinction between in- and outpatients with respect to resistance patterns?

*Levin:* I am not a physician and I do not work with patients, but I am inclined to think that the outpatient situation is ideally dealing with community-acquired bacteria, as long as the people occupied with outpatients do not deal with intensive-care wards. You have this other ecosystem occurring where people are coming from nursing homes into hospitals. So maybe what we might want to do is to separate those who are coming from another institution into an outcare environment, from those who are truly coming from the community.

*Verbrugh:* Could you explain how you go about making your models? You started out making some assumptions. Do you do that with a group, and who are in that group?

*Levin:* With my own group. One of my demands when I moved to Emory was to have a coffee room with a blackboard, and we sit around there, and I think probably more papers came out of that room than from the labs. We sat around when we read that paper by Weaner et al, and I said, how do you explain this phenomenon? And then we made that model. Sometimes we have been asked to make models. For example, we just made one for SmithKline Beecham on a grant to look at penciclovir resistance, but most of the time we sort of hang out and talk about models. This is a lot easier than working.

*Verbrugh:* I was wondering about that, because some of these assumptions come from biology, from medicine. What type of input do you get in those blackboard discussions?

*Levin:* One of the things that are very nice about being at Emory is that we have friends from the CDC coming over – other physicians, George McGowan and others – so we are not totally isolated from biology and medicine. We read the literature, we go to ICAAC. I think it is very revealing. We did a paper with Sebastian Bonhoeffer and Marc Lipitch on cycling, since everybody thinks cycling of antibiotics is a good thing to do. So we did some modelling, and it turned out that in that model cycling was a bad idea. It is my impression that there are a lot of intuitive approaches to antibiotic use, including questions of within-host dynamics. We are doing work on the within-host dynamics of treatment. How do you determine the dose and so on? Well, there are the neutropenic mice and MICs and areas-under-the-curve, but most of that kind of consideration is done in the absence of any consideration of the host response. If we are modelling things with the host response, we speak to you guys.

*C. Vandenbroucke-Grauls:* Would it be an idea to invite Marc and Daren to your coffee room and for you to join the two models for the ICU together? The model without antibiotics and the antibiotic model. Would it be difficult to put the two models together into one model?

*Levin:* No, some of the models are very similar in fact. A model makes it very clear what your assumptions are, and if different groups are making different models, that is a very positive thing. For the most part using different models, we get the same results. We did a model on HIV. The question was whether HIV treatment would make the AIDS epidemic worse. There was a paper done in 1991 by Anderson, Gupta and May, arguing that treatment of HIV could in fact make the epidemic worse. Our group, using a very different model, came to a similar conclusion. A recent paper by Quinn et al. showed that with low HIV viral loads they did not get any transmission at all. When you put that into the model, it comes out rather in favour of treatment. I think it is like anything else in science. When you are publishing these modelling papers and other people publish other modelling papers, you could check to see the generality of assumptions looking at different kinds of models.

*Van der Meer:* I would like to come back to the point about antibiotics to which there is no resistance. This, of course, has been a very optimistic thought. Almost every pharmaceutical company once had such a new antibiotic and this optimism. You can still read similar claims in the literature occasionally. A couple of years ago there was a Lancet paper discussing new options for antibiotics. These authors also claimed that there would not be resistance to this class of antibiotics. If you wait long enough, of course, you will see the evolution of resistant micro-organisms. So do you need more boxes downwards in that scheme as a function of time?

*Levin:* I agree that resistance is going to be a matter of time. I think it would be worth looking at in a model. There are two possibilities. Which would be the better use of a new antibiotic? Would it be better to just use it fully, then wait for resistance to develop? Or had you better keep it in store and only use it for serious cases? There is a sense of optimism about this right now. 90-95% of antibiotic therapies are empiric. I think if resistance became really problematic, not just Newsweek saying so, but people starting to die of infections that would previously have been treatable, I think we all would change our perception. We are now approaching the technology that will enable us to identify bacteria very quickly. I think we can go from empiric therapy to directed therapy. There could be an increasing market for narrow-spectrum antibiotics.

*Van der Meer:* If you do the modelling for a class of antibiotics to which no resistance exists, should you withhold that antibiotic? It probably depends very much on whether that particular drug is a broad-spectrum drug or a narrow-spectrum drug, a very targeted drug versus a

drug which would wipe out many species of micro-organisms, because, once you have wiped out all the bacteria, of course the fungi are still there. This is what we see happening with carbapenem use in hospital settings, where you can actually predict what is going to happen once you have exposed the patients and the ward to enough carbapenems.

*Levin:* All these questions are ideal for modelling, and, as I pointed out, modelling is cheap and probably modellers are relatively cheap too. So I think these questions should be addressed. I think it is an ideal question to be asked in these other contingencies. The biggest problem I see is trying to get the data that we need: what, for example, is the relationship between resistance and transmission? We cannot get those data. We could easily estimate the cost of fitness competition in the lab, and in mice and so on, but we would love to get the transmission data and all that. I think the models, if they are used right, can be very useful if we could get the real data to estimate the parameters and then independently estimate the parameters and see if the models are in the right ballpark.

*Van Wijngaarden:* There was a presentation at Atlanta recently, at the conference on re-emerging infections. It was about the common practice in hospitals of limiting the variety of antibiotics specialists are allowed to use. The presentation stated that this is actually bad policy. You had better allow for a wide variety of antibiotics to be used, because after a while that gives a lesser risk of a resistance problem in the hospital. You end up in a much worse situation than if you allow a wider variety of antibiotics to be used right from the beginning. Is your modelling of any use in testing this hypothesis?

*Levin:* We actually are addressing that very question of what is the optimal use of multiple antibiotics. We also looked into the question of optimal use in communities. We made a model with Sebastian Bonhoeffer. There was a question of whether you are better off cycling or simultaneously using two antibiotics, and simultaneous use turned out to be better there. I think that the complication there is going to be cross-resistance and plasmid-borne resistance. It is not as if we are only dealing with resistance resulting from mutation and selection: much of it is plasmid-borne and multiple resistance. Another problem with a broad-spectrum antibiotic is that you are not only clearing a large flora, but you are also making it that much easier to evolve resistance, resistance that will ultimately be transmissible. That is another thing one might worry about, that if it just has the entire flora under selection pressure you almost certainly are going to make resistance more likely than if you only had one species under selection.