

Minimizing Potential Resistance: A Population Dynamics View

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I examine the results of studies that used mathematical models of the epidemiology and population genetics of antibiotic treatment and resistance in open communities and in hospitals to explore the following issues: the relationship between antibiotic consumption and the frequency of antibiotic resistance in bacterial populations in communities and in hospitals; methods of controlling the growth, dissemination, and persistence of antibiotic resistance in these settings; the extent to which resistance can be controlled; and the speed with which the effects of control measures will be realized. In open communities, it will take years or even decades to see substantial reductions in the frequency of antibiotic resistance solely as a result of more prudent (reduced) use of antibiotics. However, if we can restrict the input of resistant bacteria into hospitals, through the application of infection control and other measures, it should be possible to reduce the frequency of resistance and even eliminate resistant bacteria from these institutions in short order.

It is clear that the widespread evolution, dispersal, and maintenance of genes and accessory elements coding for resistance to antibiotics in the pathogenic and commensal bacteria of humans and domestic animals can be attributed to the use of these agents for treatment and prophylaxis in humans and for growth promotion in livestock. It is also clear that the frequency of resistance in bacteria and the number of different antibiotics to which individual bacteria are resistant are directly related to the consumption of these agents and the patterns in which different agents are used [1–6]. Not so clear is whether we can substantially reduce the frequency of antibiotic resistance in bacteria by controlling the consumption of antibiotics and modifying the patterns of use of different antibiotics. Also not clear is how much time it will take before the effects of these interventions will be realized.

In this report, I explore the problem of controlling

antibiotic resistance from the perspective of population biology. I separately consider what mathematical models of the epidemiology of drug resistance tell us about the factors contributing to the ascent of resistance in open communities and in the closed settings of hospitals and nursing homes. Based on the results of the analysis of these models, some data, and some prejudices about human behavior and social systems, I argue that it is unlikely that in countries such as the United States we will be able to control resistance in open communities solely by calling for prudent use of antibiotics. More optimistically, I argue that as long as the input of resistant bacteria into hospitals and intensive care wards can be kept low, it should be possible to dramatically reduce the problem of resistance in these institutions.

MODELS AND PREDICTIONS

Population Biology of Antibiotic Treatment and Resistance in Communities

There have been 2 basic approaches to modeling the population biology of antibiotic treatment and resistance in open communities. The first, which I shall call

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the “population genetics” approach, considers the changes in the frequencies of resistant and sensitive bacteria as functions of antibiotic use but does not formally follow the course of infections in treated and untreated hosts. The second, which I shall call the “epidemiological” approach, is in the compartment model tradition of the mathematical epidemiology of microparasites [7]. These models make specific assumptions about the transmission of antibiotic-sensitive and -resistant bacteria between hosts and the course of the infection but do not specifically consider the population dynamics of the bacteria. Needless to say, both kinds of models are no more than caricatures of the population biology, ecology, and genetics of antibiotic treatment and resistance. Their role is not to provide precise analogues of these processes in real communities, but rather, in a quantitative manner, to (1) evaluate the consequences of antibiotic treatment and prophylaxis on the epidemiology of bacterial infections, (2) identify and evaluate the relative contributions of different factors responsible for the ascent and persistence of resistance, (3) facilitate the interpretation of epidemiological data on antibiotic consumption and resistance, (4) generate testable hypotheses about the factors responsible for observations about antibiotic resistance and consumption, and (5) design and evaluate antibiotic use protocols that maximize the epidemiological benefits of antibiotic use and minimize the frequency of resistance.

Population genetics models. To illustrate the population genetics approach to modeling resistance, I use the model for resistance in commensal bacteria developed by Levin et al. [8]. In this model, we assume that individual humans acquire and donate resistant and sensitive bacteria from and to a common reservoir at rates g and f , respectively. In the absence of treatment, resistant bacteria are at a selective disadvantage; in both the extra-host environment and in infected hosts, their fitness relative to sensitive bacteria is $(1 - s):1$, where s is the fitness cost associated with resistance, or the selection coefficient, $0 \leq s \leq 1$. A selection coefficient of $s = 0.01$ means that in a particular environment, resistant bacteria grow at a rate 1% less than that of bacteria susceptible to the antibiotic. In the absence of antibiotic treatment, the frequency of the resistant genotypes in people and the environment declines at a rate proportional to the product of the relative frequencies of the sensitive and resistant genotypes, p and q , and the selection coefficient, s , ($dq/dt = -pqs$). The frequency of resistance increases only in hosts undergoing treatment. In this simple version of the model, we assume that when a host undergoes treatment, the frequency of resistance in that patient immediately ascends to unity and then declines at the general rate when treatment ceases and that host is infected with sensitive bacteria. For a more general consideration of the frequency of resistance in treated patients, see the population genetics model in [9].

If this infection and selection process continues for some

time, eventually an equilibrium will be reached at which the rate of loss of resistant bacteria because of their lower fitness will be exactly equal to the rate at which they increase because of the treatment of individual hosts. The frequency of resistance at equilibrium will be directly related to the rate at which individual humans are treated, T , and inversely related to the fitness cost associated with resistance, s . In this model, if people receive antibiotic treatment twice annually, and resistance reduces the fitness of bacteria by 4% ($s = 0.04$), the expected frequency at equilibrium of resistant bacteria in the community at large is anticipated to be approximately 0.40. With treatment every second year, the anticipated equilibrium frequency of resistance would be approximately 0.12. If the fitness cost of resistance were lower, $s = 0.01$, then corresponding frequencies of resistance would be approximately 0.90 and 0.30 for treatment twice annually and every second year, respectively [8].

In another population genetics model of antibiotic treatment and bacterial resistance, Austin et al. [10] consider the community as a whole without considering the dynamics of treatment and infection in individual patients. They assume that the overall rate of treatment (consumption of an antibiotic) declines as the frequency of resistance to that antibiotic increases. Once again, as long as the fitness burden of resistance in the absence of antibiotics is low (1% in their examples), seemingly modest rates of antibiotic use (25 defined daily doses per 1000 patients) will lead to a rapid rise of resistance to equilibrium frequencies in excess of 50%. The message is clear, as demonstrated by these population genetics models: if resistance imposes only a slight cost to the fitness of bacteria, relatively little antibiotic use would result in the emergence and persistence of a substantial frequency of resistance.

Epidemiological models. In figure 1, I present the simple epidemiological model of antibiotic treatment and prophylaxis introduced in [11]. Hosts are of 3 states: uninfected (S), infected with antibiotic-sensitive bacteria (IS), and infected with resistant bacteria (IR), where S, IS, and IR are the densities as well as designations of hosts in these states. The fitness of sensitive and resistant bacteria is reflected in (1) the rate of transmission to uninfected hosts, β_S and β_R (bacteria with a higher rate of transmission have greater fitness); (2) the fraction of the S population receiving prophylaxis, p , and the fraction of the IS population receiving treatment, f (resistance increases with more frequent administration of treatment and prophylaxis); and (3) the rates of clearance, ν_{SU} , ν_{ST} , and ν_R (bacteria that clear more slowly have greater fitness), for untreated and treated IS hosts and for IR hosts, respectively. The reciprocals of the clearance rates, $1/\nu_{SU}$, $1/\nu_{ST}$, and $1/\nu_R$ are durations of infectiousness and thus represent the period of time in which hosts transmit the bacteria. It is assumed that treatment will have no effect on the rate of clearance in hosts infected with resistant bacteria and that there are no mixed infections or acquired

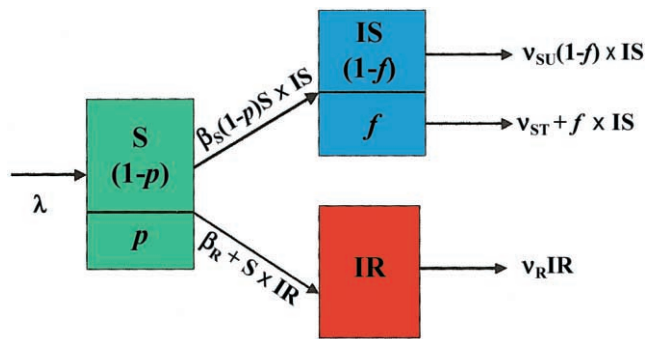


Figure 1. Compartment model for the epidemiology of antibiotic therapy and resistance in a community. S, density of uninfected individuals; IS, density of individuals infected with antibiotic-sensitive bacteria; IR, density of individuals infected with antibiotic-resistant bacteria; β_S and β_R , transmission rate parameters for sensitive and resistant bacteria, respectively; ν_{SU} , ν_{ST} , and ν_R , rates of clearance of infection in untreated patients infected with antibiotic-sensitive bacteria, in treated patients infected with antibiotic-sensitive bacteria, and in patients infected with antibiotic-resistant bacteria, respectively; f , rate of treatment; p , rate of prophylaxis; λ , rate of input of uninfected hosts (in the analysis of the properties of this model, we assume the population is at steady state, so that the rate of input of uninfected hosts is equal to the rate at which infected hosts are cleared, $\lambda = IS[1 - f]\nu_{SU} + ISf\nu_{ST} + IR\nu_R$). Model first presented in [8].

resistance. Consequently, in this model, the competitive performance of sensitive and resistant bacteria in hosts does not contribute to their fitness.

In my analysis of the properties of this model, I assumed that treatment accelerates the rate of clearance of sensitive bacteria ($\nu_{ST} > \nu_{SU}$) and that resistant bacteria are more rapidly cleared than sensitive bacteria in hosts who are not undergoing treatment ($\nu_R > \nu_{SU}$) and/or are less transmissible, $\beta_S > \beta_R$. Were these conditions not met, resistance would ascend and persist in the absence of treatment or prophylaxis. When these conditions are met, the resistant bacteria can only become established when the rate of treatment or prophylaxis exceeds a threshold value, which for treatment alone is $f > (\nu_R \beta_S / \beta_R - \nu_{SU}) / (\nu_{ST} - \nu_{SU})$ and for prophylaxis alone is $p > 1 - \nu_{SU} \beta_R / \nu_R \beta_S$ [11].

As this model is now conceived, if resistant bacteria can invade at all, they will replace the sensitive bacteria. The model can, however, be modified to account for the stable persistence of both sensitive and resistant bacteria. One way to do this is by allowing for mixed infections and acquired resistance [10, 12]. Another way to maintain both sensitive and resistant bacteria is by assuming that the host population is heterogeneous and composed of semi-isolated subpopulations undergoing different levels of treatment. Although the level of treatment and/or prophylaxis may be too low to maintain resistance in one subpopulation, it can be more than sufficient to maintain it in another and in the community at large.

The qualitative predictions of this model are consistent with

what one would anticipate intuitively: (1) Treatment and prophylaxis can reduce the overall incidence of infections and actually lead to the elimination of a particular microbe from the host population. (2) The threshold at which prophylaxis or treatment favors resistance declines with the efficacy of the drug, as measured by the relative rate at which treated and untreated patients who carry susceptible bacteria are cleared of the infection, $(\nu_{ST} - \nu_{SU}) / \nu_{SU}$, and with the fitness costs of resistance, as measured by the relationship between ν_R , ν_{SU} , and ν_{ST} , and β_R and β_S . (3) The rate of ascent or descent of resistance depends on the absolute value of the difference between the level of treatment or prophylaxis and the threshold value. This last result is illustrated in figure 2, for a situation involving an effective drug that reduces the term of infection by 80% ($\nu_{SU} = 0.10$ and $\nu_{ST} = 0.50$ per day) and in which the cost of resistance is 20% ($\nu_R = 0.12$ per day). With these parameters, the threshold rate of treatment is $f_T = 0.005$ per person per day. That is, if $>0.5\%$ of patients infected with susceptible bacteria (IS) are treated per day, resistance will increase. If 2% of the patients infected with susceptible bacteria (IS) are treated per day ($f = 0.02$ per person per day), within 4 years, the frequency of resistance is anticipated to increase from 10^{-6} to 10^{-1} (figure 2A). On the other hand, once established, the rate of decline in resistance, even with a complete cessation of antibiotic use, is going to be relatively slow and almost negligible if the rate of treatment, f , is even close to the threshold rate of treatment, f_T (figure 2B).

Confronting the data. In itself, the observation that there is a direct relationship between antibiotic use and the frequency of resistance in different geographic areas [1–6] does not necessarily mean that reductions in antibiotic use will be reflected as declines in the frequencies of resistance. It could be that the rate of ascent of resistance in regions (countries) with lower rates of antibiotic consumption and currently lower frequencies of resistance is simply lower than that in regions where antibiotic consumption is greater. Also, the frequencies of resistance in countries with lower rates of antibiotic use will eventually achieve the levels currently observed in high-use countries. More compelling evidence that resistance can be controlled by reducing antibiotic consumption comes from studies in which resistance was monitored and observed to decline following reductions in antibiotic use [4, 13–16]. But, in these studies, it is still possible that the decline in the frequency of resistance can be attributed to factors other than reductions in antibiotic consumption, for example, changes in the distribution of clones due to immunological or ecological processes that have little or nothing to do with antibiotic use. Mathematical models provide a way to actually evaluate the factors responsible for these changes in the frequencies of resistance. In their article on this subject, Austin et al. [10] used an epidemiological model to evaluate the factors contributing to the changes in frequen-

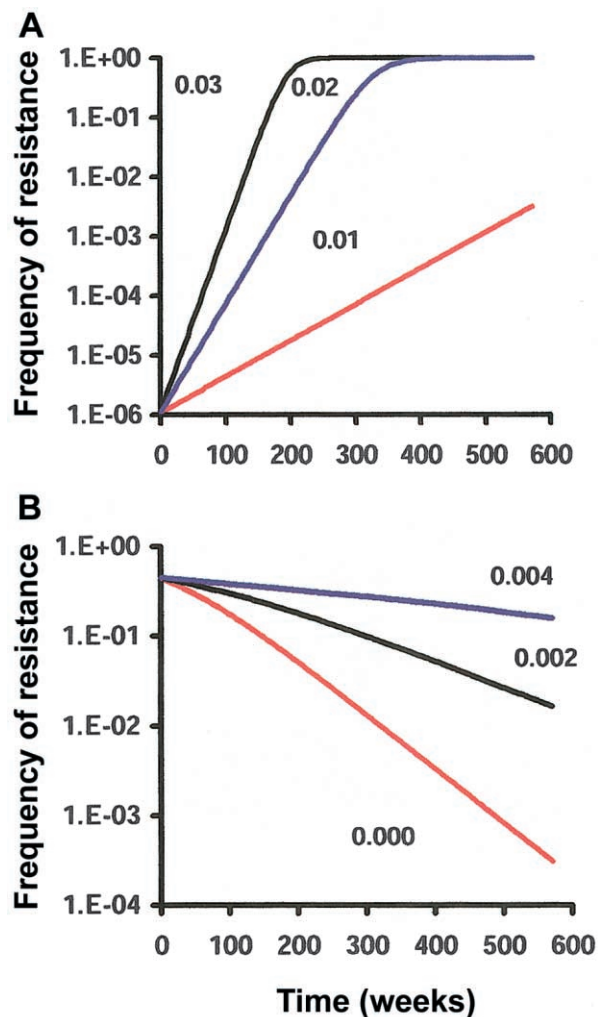


Figure 2. Compartment model for the epidemiology of antibiotic treatment and resistance in the community. The ascent (A) and descent (B) of resistance with different levels of treatment. $\beta_S = \beta_R = 10^{-6}$; $\nu_{SU} = 0.10$; $\nu_{ST} = 0.5$; $\nu_R = 0.12$; $P = 0$. Levels of treatment are noted in the figures. β_R and β_S , transmission rate parameters for resistant and sensitive bacteria, respectively; ν_R , ν_{ST} , and ν_{SU} , rates of clearance of infection in patients infected with antibiotic-resistant bacteria, in treated patients infected with antibiotic-sensitive bacteria, and in untreated patients infected with antibiotic-sensitive bacteria, respectively.

cies of resistance seen in studies performed in Iceland and Finland. With a combination of independently estimated and fitted parameters, their model provides a reasonably good approximation of the trajectories of changes in the frequency of resistance. Although at one level this approach could be criticized as “curve fitting,” that criticism misses the considerable utility of their model and its analysis, that is, the generation of specific predictions about the magnitude of the parameters governing the changes in the frequencies of resistant bacteria. If this model does account for observed changes in the frequencies of resistance in these countries, then independent estimates of

the currently fitted parameters, such as the fitness of resistant strains in mixed infections with sensitive bacteria, should be consistent with those anticipated.

The cost of resistance. As seen from the preceding, the single most important biological (rather than human-manipulated) parameter determining the rate of ascent and frequency of resistant bacteria in the community is the burden the resistance-encoding genes and accessory elements impose on the fitness of the bacteria. If there were no fitness burden associated with resistance, even the most limited use of antibiotics would result in the ascent and persistence of high frequencies of resistant bacteria in populations of commensal and pathogenic bacteria exposed to these agents. But does resistance impose a fitness cost, and what is the magnitude of those costs? How rapidly and to what extent will natural selection reduce those costs?

We would anticipate that antibiotic resistance would impose some reduction in fitness of a bacterium due to the energetic or other costs of DNA replication, protein synthesis, the expression of novel and modified proteins, and/or the effects of accessory elements on cell replication. Indeed, in competition experiments between otherwise isogenic sensitive and resistant bacteria, *in vitro* and *in vivo* (primarily laboratory mice), one can commonly, but not invariably, observe significant fitness burdens associated with novel resistance-encoding genes and plasmids. However, by maintaining these lower-fitness resistant populations in the presence and absence of antibiotics, the ascent of compensatory mutations that ameliorate the fitness costs of resistance without any reduction level of resistance can also be observed; for a review, see Andersson and Levin [17]. One interpretation of these experimental studies is that not only has widespread antibiotic use selected for the evolution, dissemination, and maintenance of resistance-encoding genes and accessory elements, but this not-so-natural selection has also led to the amelioration of the cost that these resistance genes and elements may have initially imposed on bacteria.

To date, most studies of the fitness costs of antibiotic resistance have been performed experimentally with, primarily, laboratory strains of bacteria and R-plasmids and have been restricted to evaluating the cost that resistance imposes on competitive performance. We know very little about the effects of antibiotic resistance on the relative rates at which sensitive and resistant bacteria are transmitted and cleared. Thus, at this stage, other than to say that resistance would be expected to impose some fitness cost, we are not in a position to say much about the magnitude of those costs in natural populations of bacteria or the extent to which those costs have been (or will be) ameliorated by evolution. Until we have independent estimates of these fitness parameters, it will be difficult to interpret data on epidemiology and population genetics of resistant bacteria in humans, domestic animals, and the environment. We will also be limited in our ability to predict, in a quantitative

way, the effects that different antibiotic-use regimens will have on the frequency and distribution of resistance in the community or to rationally design these regimens.

Epidemiology of Antibiotic Treatment and Resistance in Hospitals

A mathematical model of antibiotic treatment and resistance in hospitals. Whereas the absolute level of consumption of most antibiotics is greater in the community than in hospitals, the per capita consequences of antibiotic resistance on morbidity and mortality in hospitals are more profound than those in the community. The epidemiology of antibiotic treatment and resistance in these closed settings is also different from that in the community. In these institutions, the use of antibiotics for treatment and prophylaxis is more common than it is in the community, but it is also more contained and, presumably, more readily controlled. This can be seen from the simple mathematical model of epidemiology of antibiotic treatment and resistance in hospitals used by Lipsitch et al. [18] (figure 3). In this compartment model, patients are of 3 states: (1) colonized by a nosocomial pathogen, such as *Enterococcus* or *Staphylococcus*, that is sensitive to an antibiotic (drug 1) used in the hospital (S); (2) colonized by resistant forms of these bacteria (R); and (3) uncolonized by these bacteria (X), where S, X, and R are the densities of these populations as well their designations. We assume that among the patients entering the hospital, a fraction of them are uncolonized (λ_x), a fraction are colonized with a population of bacteria sensitive to the 2 antibiotics (drug 1 and drug 2) used in the hospital (λ_s), and a fraction are colonized with a bacteria resistant to drug 1 but sensitive to drug 2 (λ_r), so that $\lambda_x + \lambda_s + \lambda_r = 1$.

Uninfected (X) individuals are infected by antibiotic-sensitive and -resistant bacteria at rates proportional to the product of their density, that of the S or R populations, and a transmission rate parameter (β). We assume that S individuals cannot be superinfected with resistant bacteria and R individuals cannot be superinfected with sensitive bacteria—that is, bacteria are only able to colonize patients of the uncolonized (X) state. (To examine the results when this assumption is relaxed, see [19].) Patients colonized with susceptible and resistant bacteria, S and R, are cleared of these potential nosocomial pathogens and enter the X state spontaneously, at rate γ per day, or through antibiotic treatment and prophylaxis, at rates τ_1 and τ_2 per day for drugs 1 and 2, respectively. Because they are resistant to drug 1, individuals of the R type can only be cleared of the infection spontaneously or by treatment with drug 2. For convenience and for the economic well-being of this model hospital, we assume that the rate at which patients enter the hospital is exactly equal to the rate at which they leave (healthy or otherwise).

Results. I refer the reader to reference [18] for a more detailed and formal (an euphemism for mathematical) analysis

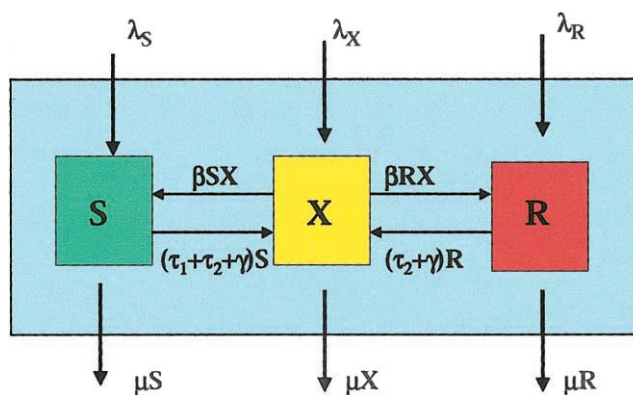


Figure 3. Compartment model of the epidemiology of resistance in a hospital. S, frequency of patients infected with antibiotic-sensitive bacteria; X, frequency of uninfected patients; R, frequency of patients infected with bacteria resistant to drug 1; λ_s , λ_x , and λ_r , fraction of patients of these states entering the hospital per day ($\lambda_s + \lambda_x + \lambda_r = 1$); μ , rate of turnover of patients per day (in the analysis of the properties of this model, we assume that the numbers of patients entering and leaving the hospital are equal); β , rate constant of transmission of sensitive and resistant bacteria; τ_1 and τ_2 , rates of clearance due to treatment with drug 1 and drug 2, respectively; γ , rate of spontaneous clearance. Model first presented in [18].

of the properties of this model. For the present consideration, I summarize the main results of that analysis, provide intuitive explanations for these results, and use numerical solutions for these equations to illustrate the dynamics of the processes under consideration.

1. *Bacteria resistant and susceptible to drug 1 can coexist in the institution, with the frequency of patients infected with drug 1-resistant bacteria being directly related to the rate at which that drug is used.* As long as a fraction of the entering patients carry sensitive bacteria, no matter how frequently patients are treated with antibiotics, there will always be a population of patients with antibiotic-sensitive flora. If the frequency of patients treated with drug 1 is sufficiently high, the rate at which uninfected patients acquire resistant bacteria that are present in the hospital will exceed the rate at which they lose these bacteria, and resistance will persist. The level at which resistance persists will increase with the rate at which patients are treated with this drug.
2. *Treatment with drug 2 (for which there is no resistance) can reduce the hospital-wide frequency of resistance to drug 1 (for which there is resistance).* Treatment with drug 2 increases the rate at which patients carrying bacteria resistant to drug 1 are cleared of their infections and converted into the uninfected state.
3. *The frequency of resistance can be reduced and resistant bacteria actually eliminated in at least 5 ways:*

- a. *By reducing the rate of use of antibiotics for which there is resistance.* The effect of this would be to reduce the rate at which patients carrying sensitive bacteria are

converted into the uninfected state and thus subject to colonization by resistant bacteria present in the hospital.

b. *By reducing the overall rate of transmission of bacteria in the hospital.* This too reduces the likelihood that people in the hospital who are uncolonized by these potential pathogens will be infected with resident resistant bacteria.

c. *By increasing the rate of turnover (reducing the term of stay).* This reduces the amount of time available for patients who are uncolonized by potential nosocomial pathogens to be infected by resistant strains of these bacteria that are present in the hospital.

d. *By increasing the rate of use of a drug for which there is no resistance.* The effect of treatment with this drug is to increase the rate of clearance of resistant bacteria.

e. *By increasing the rate at which patients with susceptible bacteria enter the hospital.* The introduction of patients who carry sensitive bacteria is the reason that resistance does not take over in hospitals that have high rates of antibiotic use. It is also the reason for the relatively rapid rates of decline in the frequency of resistance after reductions in antibiotic use and other interventions. In essence, susceptible bacteria from these patients replace the resistant bacteria.

4. *For the individual patient, treatment with drug 2 is a risk factor for the carriage of bacteria resistant to drug 1.* This can be seen if the diagram of the present model is modified to allow separate consideration of patients who have and patients who have not been treated with drug 2 [18]. Patients colonized with either sensitive or resistant bacteria can be cleared of the infection by treatment with drug 2, for which there is no resistance. As a consequence, patients with susceptible flora who are treated with drug 2 are more likely to be converted to the uncolonized state and thus are more likely to be infected with resistant bacteria than those who have not been treated with this drug. One interpretation of this is that for an individual, treatment with a drug for which there is no resistance is a risk factor for colonization with resistant bacteria. For a population, on the other hand, treatment with that drug could be an asset, because it would reduce the overall frequency of resistance in the hospital.

Kinetics. It is of interest to compare the rates at which the frequency of resistance in hospitals responds to changes in the frequency of antibiotic use (and other interventions) with the anticipated rate at which the frequency of resistant bacteria in communities responds to changes in the frequency of antibiotic use. The rate of ascent of resistance increases with more frequent use of drug 1 (figure 4A). If the rate of antibiotic use is below the threshold for the ascent of resistance, the rate of decline in the frequency of resistance decreases with the rate

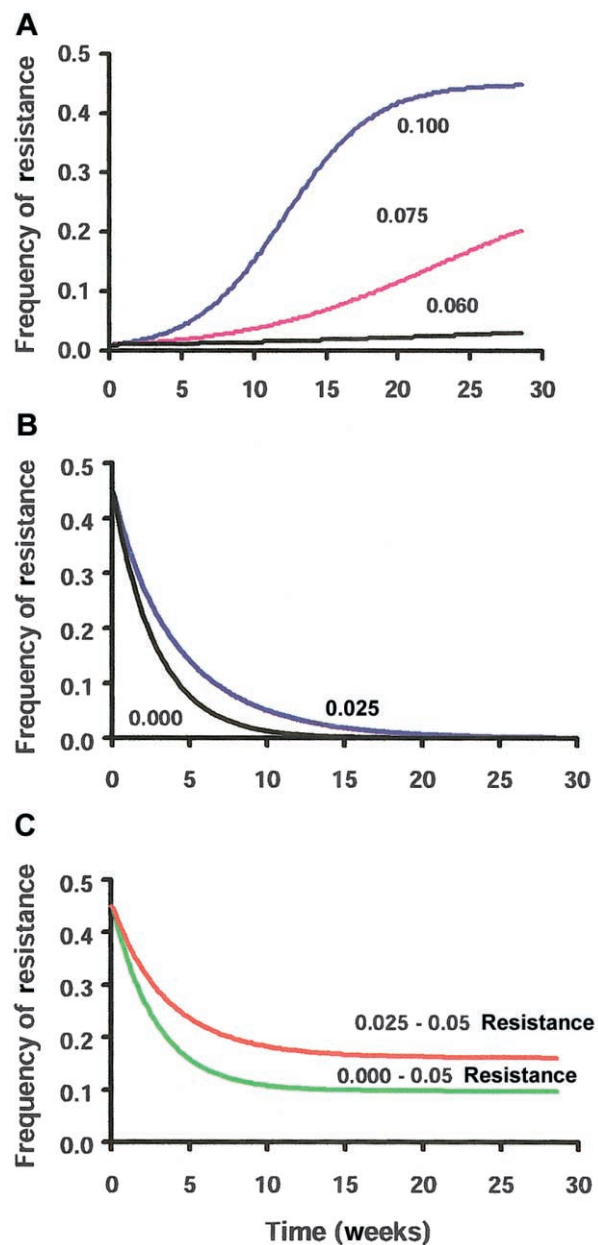


Figure 4. Model for the epidemiology of antibiotic treatment and resistance in hospitals. Changes in the frequency of resistance with different levels of treatment with drug 1, τ_1 ($\tau_2 = \gamma = 0$). $\beta = 10^{-2}$; $\mu = 0.10$. The steady state density of the hospital is maintained at 200 patients. The numbers in (A) and (B) are the rates of treatment, and those in (C) are the rates of treatment and the frequency of resistant bacteria entering the hospital. A, Ascent of resistance. B, Decline of resistance in a situation in which no resistant bacteria enter the hospital, $\lambda_s = \lambda_x = 0.50$ and $\lambda_r = 0.00$. C, Decline in the frequency of resistance when 5% of the patients entering the hospital carry resistant bacteria, $\lambda_s = 0.45$; $\lambda_x = 0.50$; $\lambda_r = 0.05$. β , rate constant of transmission of sensitive and resistant bacteria; γ , rate of spontaneous clearance; λ_r , λ_s , and λ_x , fraction of patients infected with resistant or susceptible bacteria or of uninfected patients, respectively, who enter the hospital per day; μ , rate of turnover of patients per day (in the analysis of the properties of this model, the numbers of patients entering and leaving the hospital are equal); τ_1 and τ_2 , rate of clearance due to treatment with drug 1 and drug 2, respectively.

of antibiotic use (figure 4B). If no resistant bacteria enter the hospital, the frequency of resistance in the hospital will decline to negligible levels in weeks, rather than years or even decades, as is anticipated in the community (compare figures 4B and 2A). This is mainly because there is a continuous flow of patients carrying susceptible bacteria in the hospital, and not because there is a fitness cost associated with resistance. In this model, we are assuming that resistance imposes *no* cost on bacterial fitness. If, however, a fraction of the patients enter the hospital with resistant bacteria, the frequency of resistance to that antibiotic in the hospital would exceed that in the community. The reason for this is that the uncolonized patients can be colonized by entering as well as by resident resistant bacteria, even in the absence of antibiotic use. This situation is further exacerbated when that antibiotic is used in the hospital, even when the rate of use is less than the threshold for the ascent of resistance in the absence of an entering population of patients carrying resistant bacteria (figure 4C). The situation would be somewhat better if the resistant bacteria were less transmissible or spontaneously cleared at a higher rate than the sensitive bacteria (i.e., had a fitness disadvantage), but not much better. Under these conditions, greater levels of antibiotic use would be needed for resistance to ascend to high frequencies, but as long as patients carrying resistant bacteria enter the hospital, resistant bacteria will always be present in the hospital.

Complications, caveats, and reality. Obviously, this model does not consider much of the reality (complexity) of the epidemiology of antibiotic treatment and prophylaxis in hospitals or the variation within and between hospitals [20]. Included among the more important of these realities is the considerable variation in the term of stay of patients and the variation in their susceptibility to infection. Patients who stay longer and are more susceptible to infection will disproportionately contribute to the resistance problem. Also not considered in this model is the fact that patients often move from hospital to hospital and from nursing homes to hospitals and back. These patients are likely to carry resistant strains of nosocomial pathogens [21]. To some extent, however, these complications (and realities) can be incorporated into these models, and their effects can be evaluated. Nevertheless, there is no reason to anticipate that the analysis of more realistic models will lead to different conclusions about the contribution of the various factors controlling the ascent of frequencies of resistance in hospitals or the relatively rapid rate at which these frequencies will respond to modification of these factors.

Indeed, the results of retrospective studies of the epidemiology of antibiotic resistance in hospitals are consistent with the predictions of this simple model. In hospitals, unlike in open communities, reductions in rates of antibiotic use are reflected in rapid changes in the frequency with which patients carry bacteria resistant to these agents [21, 22]. There is also

evidence that the use of antibiotics for which there is little resistance or cross-resistance and few linked resistance genes can reduce the frequency of infections caused by resistant bacteria [21]. Finally, as anticipated by this model, in hospitals and nursing homes, treatment with antibiotics for which there is little or no resistance, cross-resistance, or genetically linked resistance is a risk factor for resistance to antibiotics for which there are chromosomal or plasmid-encoded resistance genes [24]. Although gratifying, these or other observations consistent with the prediction of this model are not a test of its validity. For that we would need prospective studies to test, in a quantitative way, the validity of the assumptions of this model and the predictions generated from the analysis of its properties.

DISCUSSION AND CONCLUSIONS

Controlling resistance in the community. The 2 models of the epidemiology of antibiotic resistance in the community considered here are different in kind, but they, along with other models of this process, such as that in [10, 25], make the same general prediction. As long as resistance imposes some cost on the fitness of bacteria, reduction in the rates of antibiotic use can reduce the frequencies of resistance or at least slow its rate of ascent. Whether these measures will actually be able to lead to significant reductions in the frequencies of resistance in communities where it is already high depends on the magnitude of the fitness cost and the rate of use of antibiotics for which there is direct cross-resistance or associated linkage selection for resistance. Although evidence suggests that antibiotic resistance can impose some cost on the fitness of bacteria, at this juncture, it is not clear how generally this occurs or the extent to which natural selection ameliorates those costs. Nevertheless, it seems reasonable to anticipate that reductions in antibiotic consumption and changes in the patterns of use of different antibiotics will at least retard the rate of increase of resistance, buying time for the development of alternatives, and may even reduce it.

Prudence meets the tragedy of the commons. Calls for the more prudent and appropriate use of antibiotics are a reasonable and necessary way to reduce the consumption and misuse of these agents. Who can argue against prudence and appropriate use? And it is clear that with a sufficiently intense effort at promoting restrained and restricted use of antibiotics to the public, as well as to physicians, reductions in antibiotic consumption can be achieved [13–16, 26, 27]. Not so clear is whether in countries such as the United States these campaigns alone will be able to reduce antibiotic consumption sufficiently to reverse the growing tide of resistance or even slow it down. The problem was beautifully characterized in 1968 in an essay by Garrett Harden entitled “The Tragedy of the Commons” [28]. In essence, it comes down to the conflict between what

is good for the individual and what is good for the collective. As long as taking antibiotics for therapy and prophylaxis is perceived to be of little or no risk to the patient, it will be difficult to convince people not to want antibiotic treatment and physicians not to prescribe these drugs for indications for which there is even a remote chance of reducing morbidity or the likelihood of death. Currently, this situation is exacerbated by the discovery of evidence of associations between bacteria and diseases such as gastric ulcers or, even though the available evidence is insufficient, arteriosclerosis. To consider this problem more personally, ask your physician (or yourself, if you are of that profession) this question: What would you do if it were you, your child, or your grandchild who had otitis media, or you or a relative who had coronary artery disease?

The tragedy of the antibiotic commons may, however, be somewhat different from the common pasture of Garrett Hardin's 1968 essay. There may be a technical solution. The *Haemophilus influenzae* B vaccine has been successful in reducing the incidence of invasive *H. influenzae* infections [29], and conjugate vaccines for *Streptococcus pneumoniae* should soon be available [30]. If these newer vaccines are also effective, they could, or at least should, reduce the amount of antibiotics used to prevent or treat invasive diseases caused by these microbes, such as that in day care centers. I hope that before these vaccines are widely used, greater consideration will be given to their potential impact on the ecology of infections with these normally commensal organisms [31–34]. We do not want to generate new pathogens. Part of a technical solution may also come from the design and implementation of protocols for the optimal use of different antibiotics in the community. In designing these protocols, it is critical to take into account the epidemiological effects of antibiotics in reducing the overall incidence of disease, as well as the resistance problem [35]. Stemming the tide of resistance should not be the sole goal of these enterprises. Antibiotics are used for reasons other than to promote resistance.

Controlling resistance in hospitals. All the parameters of the model that was described earlier of the epidemiology of antibiotic use in hospitals are subject to control, and the model predicts that, by manipulating these parameters, the frequency of resistance to specific antibiotics can be reduced in a number of complementary ways: (1) by reducing the rate of consumption of antibiotics for which there are substantial frequencies of resistance in the institution; (2) by reducing the overall rate of transmission of bacteria between patients by promoting and enforcing barrier protection, hand washing, and other infection control procedures (using a similar model and data for vancomycin resistance in intensive care units, McLean [34] came to the same conclusion); (3) by increasing the rate at which patients leave the hospital—the rate of turnover (for economic reasons, there is already plenty of effort and pressure to do

this, and it is gratifying to realize that these very actions may also reduce the frequency of resistance); and (4) by the use of antibiotics for which there is little or no resistance. One implication of this latter prediction is that it should be possible to design antibiotic cycling regimens to even further reduce the frequency of resistance in hospitals. Perhaps the most optimistic prediction of the model considered here, as well as that of Austin et al. [36], is that the response to measures to control resistance in hospitals is anticipated to be rapid, taking place within months or even weeks, rather than decades or years, as is anticipated for open communities.

The big caveat. There is, alas, a negative prediction associated with this model of the epidemiology of antibiotic therapy in hospitals. Ultimately, the control of resistance in these closed institutions depends on the success of controlling resistance in the community. If patients who enter the hospital carry pathogens with the potential for nosocomial transmission that are resistant to the antibiotics used in that institution, the frequency of bacteria resistant to those drugs in the hospital is anticipated to be even greater than that in the community. It is also possible to control this problem by preventing entering patients with these resistant bacteria from mixing with the general hospital population before those bacteria are cleared. These cohorting procedures are already in place in Sweden and appear to have been successful [37] (also G. Kahlmeter, personal communication). Whether these procedures can be instituted in countries with different medical systems is another matter. My optimistic prediction is yes, if the problem were grave enough for these measures to be cost-effective.

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