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The Population Genetics of Antibiotic Resistance II: Analytic Theory for Sustained Populations of Bacteria in a Community of Hosts

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The phenomenon of antibiotic resistance is of practical importance and theoretical interest. As a foundation for further studies by simulation, experiment, and observation, we here develop a mathematical model for the dynamics of resistance among the bacteria resident in a population of hosts. The model incorporates the effects of natural selection within untreated hosts, colonization by bacteria from the environment, and the rapid increase of resistance in hosts who receive antibiotics. We derive explicit formulas for the distribution of resistance among hosts and for the rise or fall of resistance when the frequency of treatment is changed.

1. INTRODUCTION, BASIC IDEAS, AND NOTATIONS

Antimicrobial chemotherapy, the use of chemical agents to control infections with microparasites (bacteria, protozoa, viruses and single cell fungi), is almost certainly the single most significant achievement of interventive medicine. It is also an achievement that may well be short-lived. Ever since the first wide-scale applications of this technology 50 years ago, the frequency of microbes resistant to such chemotherapy has been steadily increasing. Virtually all of the major species of pathogenic bacteria include strains resistant to some, or in most cases a number, of the antimicrobial agents employed to control them (Bloom, 1992; Cohen, 1992; Cohen, 1994; Levy, 1994; McGowan, 1983; Neu, 1992; Tomasz, 1994). Chemotherapy-mediated selection has also led to the ascent of resistance in major protozoan parasites, like malaria, (vanEs, 1993; Skamene and Schurr, 1993) and in a number of viruses as well (Freifeld and Ostrove, 1994). During the early days of antimicrobial therapy, new or modified antimicrobial agents were discovered, developed and produced at a sufficient rate to keep up with microbes' evolving resistance. Now, however, the prognosis is substantially more dreary; "natural" selection appears to be winning the arms race with technology (Neu, 1992). It is clear that we have to husband the antimicrobial agents in our current arsenal by becoming more prudent with the use of those currently

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available. Not so clear is whether prudence will pay off in a reasonable amount of time.

To address this not-so-clear point, two questions have to be answered. What is the relationship between the rate and intensity of antimicrobial chemotherapy (treatment) and the frequency of resistant microbes? How rapidly will the frequency of resistant microbes respond to increases or decreases in the rate of treatment?

Mathematical models need to be developed to answer these questions for two distinct groups of bacteria. One group includes those bacteria which are typically transmitted from one diseased host to another (directly or indirectly) and are eventually cleared; examples include *Mycobacterium tuberculosis*, *Neisseria gonnorhoeae*, and *Vibrio cholerae*. For such bacteria, antibiotic treatment to cure the infections they cause will be the primary selective force favoring the ascent of resistance. Mathematical models have been developed to address the population dynamics of resistance in such organisms (Massad *et al*., 1993; Antia *et al*., 1997; Bonhoeffer *et al*., 1997).

A second group of bacteria in which resistance is clinically important are those bacteria that normally colonize hosts asymptomatically, typically living on the skin or in the digestive or upper respiratory tracts. Such asymptomatic carriage is often long-lived, and carriage of these bacteria is not typically cleared by the immune response of the patient or even by antibiotic treatment. This group includes a number of occasional or opportunistic pathogens, whose translocation from their normal commensal habitat into normally sterile sites, such as the blood, cerebrospinal fluid, or lungs, can cause serious disease. Among these normally commensal bacteria are a number of community- and hospital-acquired pathogens such as *Streptococcus pneamoniae*, *Staphylococcus aureus*, *Enterococcus* spp., and *Escherichia coli*. In addition to their role as pathogens, these commensal bacteria may also cause clinical problems by donating resistance genes to pathogenic bacteria (Schwalbe *et al*., 1990). Finally, commensal bacteria can serve as indicator populations, showing the extent of selection for antibiotic resistance in the community.

In an earlier report (Levin *et al*., 1997) we began to address the population biology of antibiotic resistance in such commensal populations using numerical simulations. Here we develop a formal mathematical theory to address these questions for the sustained (commensal) microbial communities of hosts treated with chemotheraputic agents.

In the mathematical theory that follows, we take as given: (a) the frequency with which hosts are treated with a particular antibiotic per unit time (A in what follows), (b) the fraction of bacteria which become resistant in a host when that host receives treatment (p^* in what follows), (c) the fraction of bacteria in the environment which are resistant (P in what follows), (d) the rate of migration of these environmental bacteria into hosts per unit time (m in what follows), and (e) the fitness cost of resistance, i.e., the coefficient of selection against resistant bacteria in untreated hosts per generation (s in what follows). We present explicit formulas in terms of these parameters for: (i) the distribution of the frequency of resistant microbes in a community of hosts as a function of the frequency and intensity of chemotherapy treatment and fitness cost of resistance and (ii) the mean prevalence of resistance averaged over all hosts. See (5.4), (6.3), (6.4), (6.6), and (6.7) for the former and (5.5), (7.1), and (7.2) for the latter. These formulas indicate that, once resistance genes are established in the environment, even large changes in their frequency may have very little effect on what happens within the host population. Thus calculations based on the unrealistic assumption (c) may nevertheless yield valid insights. We briefly discuss the implications of this theoretical analysis for the resistance problem.

The model considers a homogeneous population of individuals. All of them are hosts to populations of bacteria of a particular species. Some of these, the RESISTANTS, possess a discrete heritable resistance factor that renders them immune to the action of a certain antibiotic. The rest,

TABLE I

Symbols Used in the Calculations

Symbol	Usage
t	The time
N	The number of bacteria in each host
H	The number of hosts
p, P	The fractions of resistant bacteria in a host and in the environment
$\bar{p}$	The relative frequency of resistant bacteria averaged over all hosts
a, b	The smaller and larger roots of the quadratic in (2.2)
x	The "sensitivity," an alternative way of measuring the relative frequency of sensitive bacteria in a host—see (2.7)
u	A variable used to simplify formulas connecting p and x
p^*, u^*	Maximal allowable values for p and u—see Section 4
κ	The rate of change of x—see (2.6)
s	The selective advantage of sensitives in competition with resistants
m	The rate at which bacteria migrate from the wild into hosts
A	The average frequency of antibiotic treatment of a host
B	A/κ
$\bar{\delta}$	The average duration of treatment
$\phi(x, t)$	the "density" of hosts with sensitivity x—see Section 3
$\Phi(t)$	The number of hosts in a point concentration at the maximum possible value of p

called SENSITIVES, are assumed to be highly susceptible to the antibiotic. There is also an ambient population of so called wild bacteria of the same species in the environment. We assume that the numbers of both the hosts and of bacteria per host are fixed and that these numbers are so large that it is appropriate to deal with continuous approximations and think in terms of densities of hosts and frequencies of bacterial types rather than in terms of actual numbers.

The exact definitions of the symbols to be used will be given later as we describe the model. For convenient reference, Table I lists the most important symbols with indications as to their usage.

2. SELECTION AND MIGRATION ACTING ON A SINGLE HOST

Consider a single host. Let $p = p(t)$ be the fraction of the host's bacteria that are resistant and let $q = 1 - p$ be the fraction that are sensitive.

We assume that each sensitive bacterium produces new bacteria at a rate of α bacteria per *day* and for each new bacterium produced, one of the existing bacteria is chosen at random and eliminated. Thus the rate at which such events are eliminating resistants is αNpq per *day*. Similarly, if the resistants have birth rate β, such births will be adding resistants at a rate of βNpq.

The effect of migration of bacteria from the environment into a host is handled similarly. Let P be the fraction of the wild bacteria that are resistant. Assume that each host is invaded by randomly chosen wild bacteria at a rate of Nm bacteria per *day* and that randomly chosen bacteria from the host's population are eliminated at the same rate. Thus the net rate of change in the number of resistants attributable to migration will be $NmP - Nmp$.

Putting it all together, the rate of change in the number of resistants will be $-\alpha Npq + \beta Npq + Nm(P - p)$ and the rate of change in the fraction, p, of resistants will be

$$\frac{dp}{dt} = -spq + m(P - p) \tag{2.1}$$

where $s = \alpha - \beta$ is the selective advantage of the sensitives.

The right-hand side of (2.1) is a quadratic function of p with leading coefficient s. As p takes on the values 0, P, and 1, the right side assumes the values $mP \geqslant 0$, $-sP(1-P) \leqslant 0$, and $m(P-1) \leqslant 0$. Thus (2.1) can be rewritten as

$$\frac{dp}{dt} = s\left[p^2 - \left(1 + \frac{m}{s}\right)p + \frac{mP}{s}\right] = -s(p-a)(b-p) \tag{2.2}$$

for some $0 \leqslant a \leqslant P \leqslant 1 \leqslant b$.

Numerical calculations and formulas telling how the biological parameters (e.g., s, m, P, and p^*) relate to quantities introduced in developing the theory are discussed in Appendix A.

In this article we will consider only the situation where the frequency of resistants in the ambient population of bacteria does not change. This assumption is unrealistic, but we will show (see Fig. 6) that moderate changes in P have little effect on the behavior of the model. Thus the simplified model, which allows us to give explicit formulas should, itself, give insights about the behavior of such systems and more realistic models might start from it as a first approximation.

When P is fixed the computations are greatly simplified by introducing a new variable, x, to measure the prevalence of resistants in a single host. This is conveniently done in two steps. First use a linear fractional transformation that linearizes the differential equation. Let

$$u = \frac{p-a}{b-p} \qquad \text{and note that} \qquad p = \frac{a+bu}{1+u}. \tag{2.3}$$

Then

$$\begin{aligned}\frac{du}{dt} &= \frac{du}{dp}\frac{dp}{dt} \\ &= \frac{b-a}{(b-p)^2}\left[-s(p-a)(b-p)\right] \\ &= -s(b-a)\frac{p-a}{b-p} = -\kappa u\end{aligned} \tag{2.4}$$

where $\kappa = s(b-a) = \sqrt{(s+m)^2 - 4smP}$.

When the frequency of resistants, p, is greater than P both selection and migration will tend to lower p. On the other hand, when $p < P$ the two will work in opposite directions, with selection tending to decrease p while migration will tend to increase it. The two are in balance when $p = a$. Antibiotic treatment will steadily decrease the number of hosts with $p \leqslant a$ and there is no compensating process that will move hosts into the range $0 \leqslant p \leqslant a$. For that reason, we will ignore such hosts and consider only those hosts with $p > a$.

The second step introduces a variable that will yield a partial differential equation with constant coefficients when we consider the population of hosts. Let

$$x = -\ln(u/u^*) \qquad \text{where} \quad u^* = \frac{p^* - a}{b - p^*} \tag{2.5}$$

and p^* is the frequency of resistant bacteria in a host who is being treated with antibiotics. The quantity p^* is discussed in more detail in Section 4.

Figure 1 shows the relationship between p and x, plotting x as a function of p for two representative sets of parameter values.

It follows that $x = 0$ when $p = p^*$, $x \to \infty$ as $p \to a$, and

$$\frac{dx}{dt} = \frac{dx}{du}\frac{du}{dt} = \frac{-1}{u}(-\kappa u) = \kappa. \tag{2.6}$$

For lack of a better word, we will say that a host whose frequency of resistants is p has SENSITIVITY

$$x = -\ln\left(\frac{p-a}{b-p}\Big/\frac{p^*-a}{b-p^*}\right). \tag{2.7}$$

The sensitivity is a pure number, but for dimensional analysis the unit of sensitivity will be called the "*sen*." Note that κ is measured in *sens* per *day*.

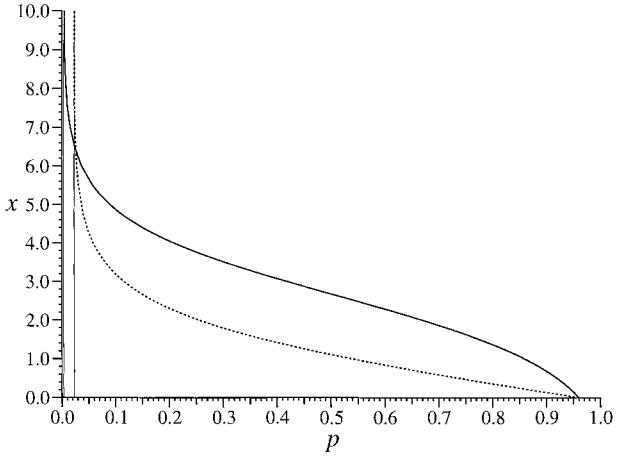

Fig. 1. The relationship between p (frequency of resistance) and x (sensitivity). Dotted line: selection coefficient $s = 2\%$ per 40 hour generation, migration rate $m = 1\%$ per day, frequency of resistants in the wild $P = 5\%$. Solid line: selection coefficient $s = 5.0\%$ per generation, migration rate $m = 0.1\%$ per day, frequency of resistants in the wild $P = 10\%$. The maximum resistant frequency, p^*, is 96% for both curves. Vertical hairlines are the asymptotes at $p = a$. For the dotted line, where m and s are nearly equal, this is only a little to the left of $P/2$, but for the solid line it is very close to zero even though P is twice as great as for the dotted line.

3. SELECTION, MIGRATION, AND ANTIBIOTIC ACTING ON POPULATIONS

In what follows we use the notation of differentials, throwing away higher order terms and interchanging the order of limiting processes wherever it is appropriate to do so.

Let $\phi(x, t)$ *hosts* per *sen* be the density of hosts with respect to sensitivity x in the sense that the number of hosts with sensitivities in the interval $(x, x + dx]$ at time t is $\phi(x, t)\, dx$. It is helpful to think of the hosts as making up a stream like a stream of cars moving along a road with milestones labeled with the value of the sensitivity.

Since the sensitivity, x, of each host is increasing at a rate of κ *sen* per *day*, hosts are entering this interval at a rate of $\kappa\phi(x, t)$ *hosts* per *day*. They are leaving the interval for two reasons. Some because their sensitivity is increasing and others because intense selection favoring the resistants causes a precipitous decline in sensitivity when a host is given the antibiotic. The former causes hosts to pass out of the interval at a rate of $\kappa\phi(x + dx, t) \approx \kappa\phi(x, t) + \kappa(\partial\phi(x, t)/\partial x)\, dx$ and the latter at a rate of $\phi(x, t)\, dxA$, where A is the rate, per *day*, at which hosts with sensitivity x receive antibiotic treatments. Then the net rate of change is $-[\kappa(\partial\phi(x, t)/\partial x) + A\phi(x, t)]\, dx$ and

$$\frac{\partial\phi(x, t)}{\partial t} = -\kappa\frac{\partial\phi(x, t)}{\partial x} - A\phi(x, t). \tag{3.1}$$

Most of the calculations will be made under the assumption that A is constant, but we will be particularly interested in what happens when A is changed from one value to another.

The characteristics of (3.1) are lines of the form $x = x(t) = c + \kappa t$. Along such a line

$$\begin{aligned}\frac{d\phi(x(t), t)}{dt} &= \frac{\partial\phi}{\partial t} + \frac{\partial\phi}{\partial x}\frac{dx}{dt} \\ &= -\kappa\frac{\partial\phi}{\partial x} - A\phi + \frac{\partial\phi}{\partial x}\kappa \\ &= -A\phi(x, t).\end{aligned} \tag{3.2}$$

If the characteristic passes through (x_0, t_0) and (x_1, t_1) then, since $c = x_0 - \kappa t_0 = x_1 - \kappa t_1$,

$$\begin{aligned}\phi(x_1, t_1) &= \phi(x_0, t_0) \exp\left(\int_{t_0}^{t_1} -A\, dt\right)\\ &= \phi(x_0, t_0)\, e^{-A(t_1 - t_0)}\\ &= \phi(x_0, t_0)\, e^{-A(x_1 - x_0)/\kappa}\\ &= \phi(x_0, t_0)\, e^{-B(x_1 - x_0)}. \qquad (3.3)\end{aligned}$$

where $B = A/\kappa$.

Note that both A and B measure the rate of decay of ϕ along a characteristic. The difference is that A gives the rate with respect to the time coordinate and B gives the rate with respect to the sensitivity coordinate.

4. BOUNDARY CONDITIONS AND EQUILIBRIA

Assume that when a host is treated with the antibiotic, the host's frequency of resistants increases immediately to a value p^*, $a \ll p^* \leqslant 1$, and remains at that value during a—possibly variable—delay of $\bar{\delta}$ *days* after which the host rejoins the stream of hosts that are steadily gaining sensitivity. This assumption implies that, in addition to the stream of hosts on the SENSITIVITY HIGHWAY, there will be a point concentration of hosts with sensitivity 0 consisting of those hosts whose delay times exceed the time since their latest treatment. The total number of hosts, H, can therefore be divided into those that are "in treatment," $\Phi(t)$, and those that are "on the highway," $\int_0^\infty \phi(x, t)\, dx$.

Although hosts with sensitivity 0 may well receive further antibiotic treatment before their sensitivity starts to decrease, we assume that $x = 0$ is the minimum possible sensitivity. Thus such treatments will not affect the host's sensitivity. It might, however, restart the delay process. Two different assumptions seem worth considering: (A) rejoining the stream is a Poisson process with mean delay time $\bar{\delta}$, or (B) the delay time is a fixed constant, $\bar{\delta}$, and treatment with the antibiotic resets the delay timer.

The situation is like that of a highway near a toll booth. Suppose cars reach the toll booth at a rate of c *cars* per *hour* and, after leaving, accelerate rapidly to a speed of v *miles* per *hour*. Then after an hour the first car will be v *miles* from the toll booth and the others will be distributed between it and the booth, giving a density of c/v *cars* per *mile*. To apply similar reasoning to the present model, we reason in terms of a very short time period so the equations need not be concerned with changes in $\Phi(t)$.

Under Hypothesis A the rate at which hosts leave the point concentration is $\Phi(t)/\bar{\delta}$ *hosts* per *day*. Hosts that leave during the time interval $[t, t + dt)$ will be spread out over the sensitivity interval $[0, \kappa\, dt)$ so the host density will satisfy the boundary condition

$$\phi(0, t) = \begin{cases} AH/\kappa = BH & \text{if} \quad \bar{\delta} = 0 \\ \Phi(t)/\kappa\bar{\delta} & \text{if} \quad \bar{\delta} > 0. \end{cases} \qquad (4.1\text{A})$$

Under Hypothesis B hosts arrive at $x = 0$ at the rate of AH *hosts* per *day*. The probability that one of these hosts will not be treated again sometime before $\bar{\delta}$ days have elapsed is $e^{-A\bar{\delta}}$, so

$$\phi(0, t) = \frac{AH}{\kappa}\, e^{-A\bar{\delta}} = BHe^{-A\bar{\delta}}. \qquad (4.1\text{B})$$

When A is not constant, the first A in (4.1B) must be replaced by $A(t - \bar{\delta})$ and the exponent must be replaced by $-\int_0^{\bar{\delta}} A(t - \delta)\, d\delta$.

Let $\hat{\Phi}$ and $\hat{\phi}(x)$ be the equilibrium values of Φ and ϕ. Then, according to (3.3),

$$\hat{\phi}(x) = \hat{\phi}(0)\, e^{-Bx} \qquad (4.2)$$

and

$$H - \hat{\Phi} = \hat{\phi}(0) \int_0^\infty e^{-Bx}\, dx = \frac{\hat{\phi}(0)}{B}. \qquad (4.3)$$

Substituting from (4.1) and solving for $\hat{\Phi}$:

$$\hat{\Phi} = \begin{cases} \dfrac{HA\bar{\delta}}{1 + A\bar{\delta}} & \text{under Hypothesis A} \\ H(1 - e^{-A\bar{\delta}}) & \text{under Hypothesis B.} \end{cases} \qquad (4.4)$$

Substituting this back into (4.3) yields the boundary value at equilibrium:

$$\hat{\phi}(0) = \begin{cases} \dfrac{BH}{1 + A\bar{\delta}} = \dfrac{HA}{\kappa(1 + A\bar{\delta})} & \text{under Hypothesis A} \\ BHe^{-A\bar{\delta}} = \dfrac{HA}{\kappa}\, e^{-A\bar{\delta}} & \text{under Hypothesis B.} \end{cases} \qquad (4.5)$$

The quantity $\hat{\phi}(0)$ will be important in what follows. In some places, formulas under the two hypotheses are identical except for which value of $\hat{\phi}$ is to be used. In other places, it is clear from the context which is intended. Explicit reference to the hypothesis is usually omitted because it would only be a distraction.

5. THE DISTRIBUTION OF RESISTANCE

Up to now, $\phi(x, t)$ has been the density with respect to the variable x, but x was introduced merely to simplify calculations. To calculate the frequency of hosts with different levels of resistance we need the density with respect to p. We will use subscripts to distinguish the two densities. Let $\phi_p(p, t)\, dp$ and $\phi_x(x, t)|dx|$ be the number of hosts in corresponding intervals $[p, p+dp)$ and $(x+dx, x]$ so

$$\phi_p(p, t)\, dp = -\phi_x(x, t)\, dx. \tag{5.1}$$

The minus sign is needed because, according to (2.3) and (2.5), x decreases when u and p increase.

In what follows we need to supplement the formulas of Section 2. From (2.5), (2.3), and (2.7), respectively, we get

$$u = u^* e^{-x}, \qquad p = \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}, \qquad \text{and}$$
$$\frac{dx}{dp} = -\frac{(b-a)}{(p-a)(b-p)}. \tag{5.2}$$

At equilibrium, (4.2) and (2.5) yield

$$\hat{\phi}_x(x) = \hat{\phi}_x(0)\, e^{-Bx} = \hat{\phi}_x(0) \left(\frac{u}{u^*}\right)^B. \tag{5.3}$$

Thus at equilibrium the density of hosts with resistant frequency p is

$$\hat{\phi}_p(p) = \frac{\hat{\phi}_x(0)}{u^{*B}} \left(\frac{p-a}{b-p}\right)^B \left|\frac{dx}{dp}\right|$$
$$= \frac{\hat{\phi}_x(0)}{u^{*B}} \frac{(b-a)}{(p-a)^{1-B}(b-p)^{1+B}} \tag{5.4}$$

where $\hat{\phi}_x(0)$ is given by 4.5.

With realistic parameter values, B tends to be quite small. So, provided the minimum at $p_{\min} = [(b+a) - (b-a)\, B]/2$ falls between a and p^*, the graph of the density $\phi_p(p)$ is a (reversed) J-curve, falling from the infinity at $p = a$ to the minimum at $p_{\min}$ and then rising to a finite value at $p = p^*$.

The frequency of resistants, averaged over all hosts, can be calculated by averaging with respect to either variable and is

$$\bar{p} = H^{-1}\left[\, \Phi p^* + \int_a^{p^*} p\phi_p(p, t)\, dp \,\right]$$
$$= H^{-1}\left[\, \Phi p^* + \int_0^{\infty} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, \phi_x(x, t)\, dx \,\right]. \tag{5.5}$$

Equation (5.5) is a special case of equations in Section 7 and numerical integration of such formulae is discussed in Appendix A.

6. DYNAMICS

In what follows there is no occasion to use ϕ_p and we will drop the subscript from ϕ_x. The value of $\phi(x, t)$ can be calculated, using (3.3), from its boundary and initial values. Thus

$$\phi(x, t) = \begin{cases} \phi(0, t - x/\kappa)\, e^{-Bx} & \text{if} \quad x \leqslant \kappa t \\ \phi(x - \kappa t, 0)\, e^{-At} & \text{if} \quad x \geqslant \kappa t. \end{cases} \tag{6.1}$$

However, the boundary conditions and the behavior of $\Phi(t)$ will depend on which of the two hypotheses we assume.

Under Hypothesis A the past history of the system is irrelevant, but under Hypothesis B the value of $\Phi(t)$ depends on arrivals and departures during the entire period from time $t - \bar{\delta}$ to time t. One situation of considerable practical interest—the only case we will consider in detail—is that where the system is essentially at equilibrium with one rate of antibiotic use and that a quite different regime is to be used thereafter. We will let $t = 0$ be the time of the change and let A be the new rate at which the antibiotic is administered while A_0 will be the earlier rate. Further, let zero subscripts indicate values at the old equilibrium.

Consider first Hypothesis A. Hosts arrive at $x = 0$ at a rate of $A \int_0^{\infty} \phi(x, t)\, dx = A[H - \Phi(t)]$ and leave at random with an average delay of $\bar{\delta}$. Thus

$$\frac{d\Phi}{dt} = AH - \left(A + \frac{1}{\bar{\delta}}\right)\Phi. \tag{6.2}$$

Hence, integrating and using (4.4),

$$\Phi(t) = \frac{HA\bar{\delta}}{1 + A\bar{\delta}} + \left[\, \Phi(0) - \frac{HA\bar{\delta}}{1 + A\bar{\delta}} \right] e^{-(A + 1/\bar{\delta})t}$$
$$= \hat{\Phi} + [\, \hat{\Phi}_0 - \hat{\Phi}\,]\, e^{-(A + 1/\bar{\delta})t}. \tag{6.3}$$

When $t=0$ the system was at the old equilibrium so (6.1) implies that when $x \geqslant \kappa t$

$$\phi(x, t) = \phi(x-\kappa t, 0)\, e^{-At} = \hat{\phi}_0(0)\, e^{-B_0(x-\kappa t)} e^{-At}$$
$$= \hat{\phi}_0(0)\, e^{(A_0-A)t} e^{-B_0 x}. \qquad (6.4A)$$

The values when $x \leqslant \kappa t$ are also conveniently expressed in terms of the equilibrium values at $x=0$. According to (4.1A), $\hat{\phi}(0) = \hat{\Phi}/\kappa\,\bar{\delta}$ and $\hat{\phi}_0(0) = \hat{\Phi}_0/\kappa\,\bar{\delta}$. Let $\Delta_{\hat{\phi}} = \hat{\phi}(0) - \hat{\phi}_0(0)$. Then (6.1), (4.1A), and (6.3), imply that for $x \leqslant \kappa t$

$$\phi(x, t) = \phi(0, t-x/\kappa)\, e^{-Bx} = \frac{\Phi(t-x/\kappa)}{\kappa\bar{\delta}}\, e^{-Bx}$$
$$= \frac{1}{\kappa\bar{\delta}} \{\hat{\Phi} + [\hat{\Phi} - \hat{\Phi}_0]\, e^{-(A+1/\bar{\delta})(1-x/\kappa)}\}\, e^{-Bx}$$
$$= \hat{\phi}(0)\, e^{-Bx} + \Delta_{\hat{\phi}} e^{-At} e^{-(\kappa t - x)/\kappa\bar{\delta}}. \qquad (6.4B)$$

Turn now to Hypothesis B.

Consider first the situation at a time t, $0 \leqslant t \leqslant \bar{\delta}$. At that time a host will be on the sensitivity highway if and only if he received no treatment between times $-(\bar{\delta}-t)$ and 0 and none between times 0 and t. These are independent events with probabilities $e^{-A_0(\bar{\delta}-t)}$ and e^{-At}. Thus the probability that any given host is on the highway is $e^{-A_0(\bar{\delta}-t)} e^{-At} = e^{-A_0\bar{\delta}} e^{(A_0-A)t}$ and the number of hosts not on the highway, i.e., the number in the point concentration, is

$$\Phi(t) = \begin{cases} H[1 - e^{-A_0\bar{\delta}} e^{(A_0-A)t}] & \text{if} \quad 0 \leqslant t \leqslant \bar{\delta} \\ H[1 - e^{-A\bar{\delta}}] & \text{if} \quad t \geqslant \bar{\delta} \end{cases} \qquad (6.5)$$

where the second line is obtained in the same way as in (4.4).

Similar reasoning shows that hosts are entering the highway at a rate of $HA_0 e^{-A_0\bar{\delta}} e^{(A_0-A)t}$ when $0 \leqslant t \leqslant \bar{\delta}$ and at a rate of $HAe^{-A\bar{\delta}}$ when $\bar{\delta} \leqslant t$. Since they move off at a rate of κ *sen* per unit time their density is

$$\phi(0, t) = \begin{cases} \dfrac{HA_0}{\kappa}\, e^{-A_0\bar{\delta}} e^{(A_0-A)t} = \hat{\phi}_0(0) e^{(A_0-A)t} & \\ \qquad\qquad \text{if} \quad 0 \leqslant t \leqslant \bar{\delta} & \qquad (6.6) \\ \dfrac{HA}{\kappa}\, e^{-A\bar{\delta}} = \hat{\phi}(0) \qquad \text{if} \quad \bar{\delta} \leqslant t. & \end{cases}$$

When $\kappa(t-\bar{\delta}) \leqslant x \leqslant \kappa t$, $t - x/\kappa < \bar{\delta}$ so

$$\phi(x, t) = \phi(0, t-x/\kappa)\, e^{-Bx} = \hat{\phi}_0(0)\, e^{(A_0-A)(t-x/\kappa)} e^{-Bx}$$
$$= \hat{\phi}_0(0)\, e^{(A_0-A)t} e^{-B_0 x}. \qquad (6.7A)$$

On the other hand, exactly the same reasoning that led to (6.4A) shows that (6.7A) continues to be valid when $x \geqslant \kappa t$.

When $x < \kappa(t-\bar{\delta})$, $t > \bar{\delta}$. By that time treatments occurring before time $t=0$ will have ceased to have any effect and $\phi(0, t)$ will be $\hat{\phi}(0)$. Thus

$$\phi(x, t) = \phi(0, t-x/\kappa)\, e^{-Bx} = \hat{\phi}(0)\, e^{-Bx} \qquad (6.7B)$$

7. THE RISE OR FALL OF RESISTANCE

In this section, we are concerned,only with frequencies and the number of hosts is irrelevant. Thus, there is no loss of generality in letting $H=1$ here, even though that would make nonsense of the reasoning in Sections 3 and 4.

Equation (5.5) is still valid. To calculate $\bar{p}$ we still average $p = (a + bu^* e^{-x})/(1 + u^* e^{-x})$ with respect to the density, ϕ_x, but the formula for $\phi(x, t)$—(6.4) or (6.7)—no longer consists of a single expression. That makes it necessary to break up the integral into several pieces.

Under Hypothesis A,

$$\bar{p} = (\hat{\Phi} + [\hat{\Phi}_0 - \hat{\phi}]\, e^{-(A+1/\bar{\delta})t}) p^*$$
$$+ \hat{\phi}(0) \int_0^{\kappa t} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-Bx}\, dx$$
$$+ \Delta_{\hat{\phi}} e^{-At} \int_0^{\kappa t} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-(\kappa t - x)/\kappa\bar{\delta}}\, dx$$
$$+ \hat{\phi}_0(0)\, e^{(A_0-A)t} \int_{\kappa t}^{\infty} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-B_0 x}\, dx. \qquad (7.1)$$

Under Hypothesis B, the dual nature of (6.7) makes it necessary to give two formulas, one for $0 \leqslant t \leqslant \bar{\delta}$ and a different one for $t \geqslant \bar{\delta}$. If $0 \leqslant t \leqslant \bar{\delta}$

$$\bar{p} = [1 - e^{-A_0\bar{\delta}} e^{(A_0-A)t}] p^*$$
$$+ \hat{\phi}_0(0)\, e^{(A_0-A)t} \int_0^{\infty} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-B_0 x}\, dx \qquad (7.2A)$$

while, if $t \geqslant \bar{\delta}$,

$$\bar{p} = [1 - e^{-A\bar{\delta}}]\, p^* + \hat{\phi}(0) \int_0^{\kappa(t-\bar{\delta})} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-Bx}\, dx$$
$$+ \hat{\phi}_0(0)\, e^{(A_0-A)t} \int_{\kappa(t-\bar{\delta})}^{\infty} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-B_0 x}\, dx. \qquad (7.2B)$$

The integrals are all very similar and, as shown in Appendix A, numerical calculations can be conveniently handled by making suitable substitutions.

8. PARAMETERS AND PREDICTIONS

We have analyzed a mathematical model of the population dynamics of sensitive and resistant bacteria living commensally in a population of hosts subject to occasional treatment with a single antibiotic. The model makes explicit predictions about both the equilibrium distribution of antibiotic-sensitive and -resistant bacteria in such a population and the time scale of changes in this distribution in response to a change in the frequency of antibiotic use.

Parameter Values: Empirical Evidence

Before describing and discussing the biological significance of the results of the models, we describe the empirical evidence relevant to estimating the appropriate ranges for several important parameters of the model: selection against resistance in untreated hosts, frequency of antibiotic treatment, bacterial generation time, environmental prevalence of resistant bacteria, the rate of migration of bacteria from the environment into hosts, and the frequency of resistants in treated hosts.

Fitness Cost of Resistance (s). The strength of selection against antibiotic-resistance genes in the absence of antibiotics has been measured in a variety of studies and depends on the bacteria, the antibiotic, the environment, and the genetics and biochemistry of resistance mechanisms (Godwin and Slater, 1979; Helling *et al*., 1981; Bouma and Lenski, 1988; Modi and Adams, 1991; Nguyen *et al*., 1989; Schrag and Perrot, 1996). At the higher extreme it has been found that the carriage of resistance plasmids can reduce fitness by as much as 50% (Godwin and Slater, 1979; Helling *et al*., 1981) and at the lower extreme, the cost of mutations to nalidixic acid resistance in another strain of *E. coli* was found to be below a measurement threshold of about 1% per generation (B.R.L., unpublished observations). Several studies have found that continued growth of resistant strains results in a rapid reduction in the cost of resistance by selection of subpopulations carrying compensatory mutations (Bouma and Lenski, 1988; Schrag and Perrot, 1996).

Treatment Frequency (A). While the use of particular antibiotics can and does vary widely, it is unlikely that on a population-wide basis any particular drug is prescribed more than twice per year per person, except perhaps in subpopulations (e.g., day care attendees and immunocompromised persons) with particularly intensive use of specific antibiotics.

Generation Time. We have chosen a bacterial generation time of 40 h. This estimate is based on the elegant calculation of Savageau (1983) that the total population of bacteria in the gut remains constant reflecting a balance between the rates of growth and evacuation. This calculation suggests that bacteria in the human gut divide at approximately 1% of their maximum rate.

The other parameters of the model—the environmental prevalence of resistant bacteria (P), the rate of migration of bacteria from the environment to hosts (m), and the frequency (p^*) of resistants in hosts immediately after treatment—are less well documented, though the experiments of Corpet (1988) might provide some basis to estimate m.

The calculations for Figs. 5–9, which show the effects of the various parameters, were made under the unrealistic assumption that $\bar{\delta} = 0$, i.e., that treatment had no duration and that hosts re-entered the sensitivity highway immediately after receiving the antibiotic. This is no great loss because a simple formula, described in Appendix B, can allow for the effect of $\bar{\delta}$.

Predictions

The model makes predictions in three general areas: (1) the frequency distribution of hosts with respect to the degree of resistance in their bacterial populations, (2) the time scale of changes in the distribution of bacteria in the host population, and (3) the way the parameters influence the average frequency of resistants in the entire population.

The frequency distribution of hosts is determined by the balance between treatment, which raises the frequency of resistant bacteria in treated hosts to 100% (or nearly so), and selection against resistant bacteria in hosts and migration of (predominantly sensitive) bacteria from the environment into hosts. Within the parameter ranges specified above the parameter B in (5.4), (6.4), and (6.7) is usually less than 1. In that case the equilibrium distribution of hosts has a vertical asymptote at a low frequency of resistance, a in the model. As the frequency, p, increases the density decreases, but the density will usually reach a minimum before p reaches p^* and then the graph will be a (reversed) J-shaped curve. If the rate of use of the antibiotic is suddenly changed, as is assumed in Sections 6 and 7, the distribution curves will consist of two parts with a sharp break at $p = (a + bu^*e^{-\kappa t})/(1 + u^*e^{-\kappa t})$ under

Hypothesis A and a discontinuity at $p = (a + bu^* e^{-\kappa(t-\bar{\delta})})/(1 + u^* e^{-\kappa(t-\bar{\delta})})$ under Hypothesis B. See Fig. 2.

Surveys of antibiotic resistance in commensal bacteria and opportunistic pathogens typically measure the resistance of one or at most a very few colonies of bacteria from each host (Johnson *et al.*, 1996). The distributions predicted by the model suggest that measuring the frequency of resistance in a large population of bacteria from each host (by selective plating, for example) would be a better way to measure the frequency of antibiotic resistance in these typically polyclonal populations. This is because most hosts will carry a mixed population, and single colony surveys can reveal only the average frequency of resistance, not the shape of the distribution. The few surveys conducted by selective plating have indeed found mixed populations within hosts (Levin *et al.*, 1997).

Figures 3 and 4 illustrate the time scale of changes in the level of resistance. They suggest that changes in the bacterial population should be evident within a time scale of years to one decade after changes in antibiotic use, provided that the selective coefficient against resistance in untreated hosts is on the order of 0.2% or more per generation and that there is a low but finite level of migration of sensitive bacteria into hosts from the environment (replacement of $> 10^{-4}$ per day is sufficient, though the time scale is considerably faster with a replacement of 10^{-2} per day).

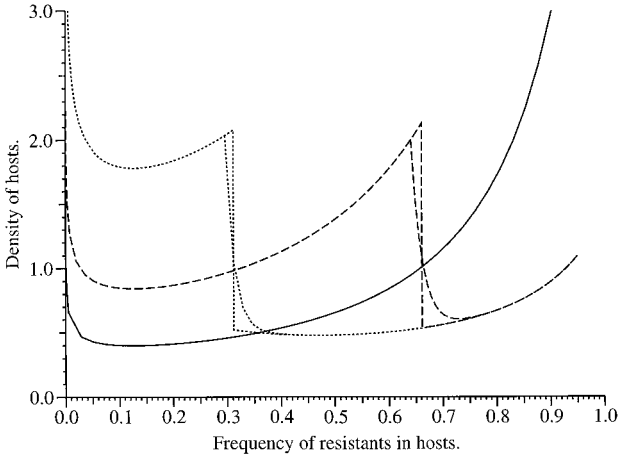

FIG. 2. The distribution of resistance in the host population and how it changes over time. The dependent variable is the density of hosts with respect to the frequency of resistants among their resident bacteria. To make comparison between Hypotheses A and B more clear, there is a vertical line joining the two halves of the curves for Hypothesis B. Solid line is the equilibrium distribution at time $t = 0$; dashed line: after six months; dotted line: after one year. Current frequency of treatment $A = 0.5$ per year. Previous frequency of treatment $A_0 = 2$ per year. Frequency of resistants in the wild $P = 0.1\%$. Mean duration of treatment $\bar{\delta} = 10$ days. Maximum resistant frequency $p^* = 99\%$.

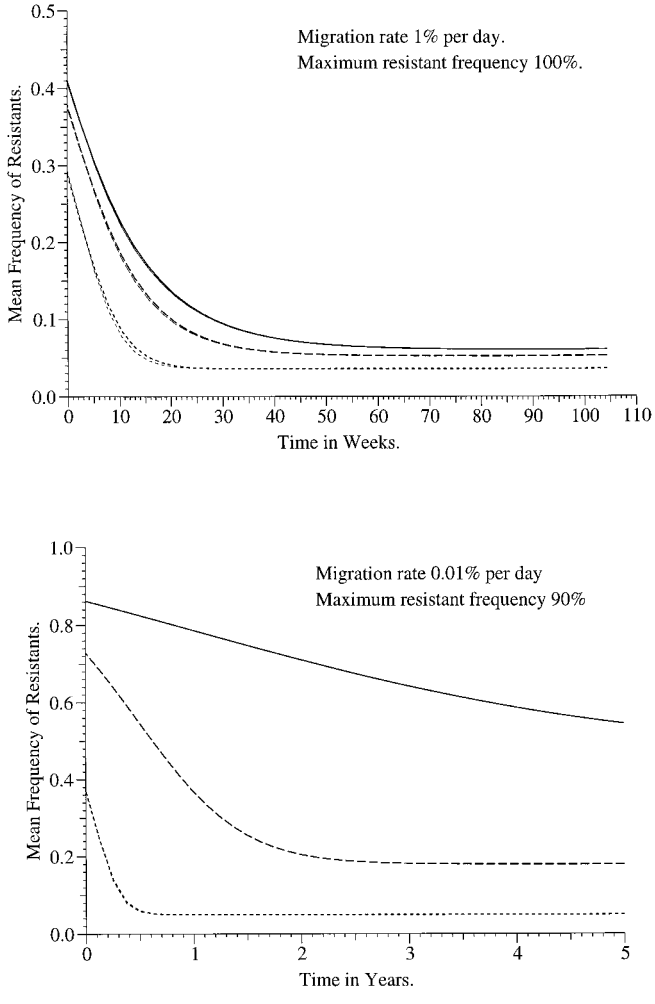

FIG. 3. The decay of resistance when the frequency of treatment is reduced. The different curves show the dependence on the selection coefficient: solid line $s = 0.2\%$, dashed line $s = 1\%$, dotted line $s = 5\%$. Previous frequency of treatment $A_0 = 2$ per year. Current frequency of treatment $A = 0.2$ per year. Mean duration of treatment $\bar{\delta} = 20$ days. The thicker lines were calculated assuming Hypothesis A and the barely discernable thinner lines assuming Hypothesis B. (A) $m = 1\%$, $p^* = 100\%$; (B) $m = 0.01\%$, $p^* = 90\%$.

The rate of change of the mean frequency of resistance will be different when antibiotic use is increased from when it is decreased (see Fig. 4). This is because the net strength of the forces causing such changes (increased treatment dominates when treatment increases, while selection and migration dominate when treatment declines) need not be the same. Similar results have been found for the decline of insecticide resistance when insecticide use stopped, which is much slower than the rise of resistance when use is instituted (Anderson and May, 1991)

Figure 5 quantifies the well-known fact that the overall level of resistance in a population can be very high when

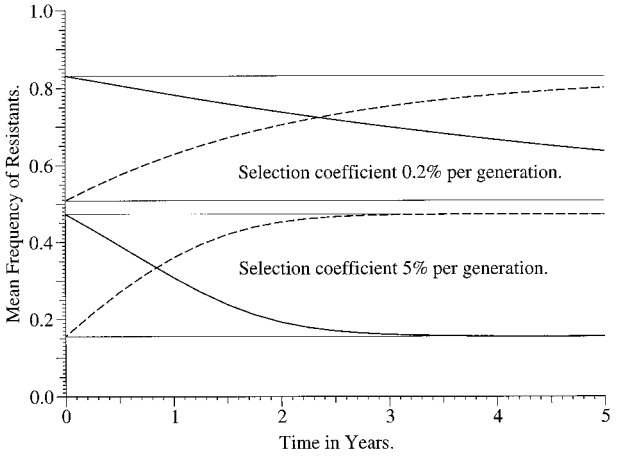

FIG. 4. Comparing the approach to equilibrium when the frequency of treatment is raised with that when it is lowered. The change is from twice a year to once every two years or *vice versa*. The solid line shows what happens when the rate is decreased from 2.0 to 0.5; the dashed lines show the behavior when it is increased from 0.5 to 2.0. Migration rate $m = 0.1\%$ per day. Frequency of resistants in the wild $P = 0.1\%$. Mean duration of treatment $\bar{\delta} = 20$ days. Maximum resistant frequency $p^* = 99\%$. Hypothesis A is assumed throughout. The thin lines show equilibrium values.

antibiotics are used indiscriminately. The assumed migration from the environment, 0.1 % per day, is sufficient to ensure that there will be enough sensitive bacteria for selection to be effective in restoring sensitivity, even when all sensitives in a host are killed by treatment. Were m very much smaller, the wide lines for $p^* = 100\%$ would be very much higher.

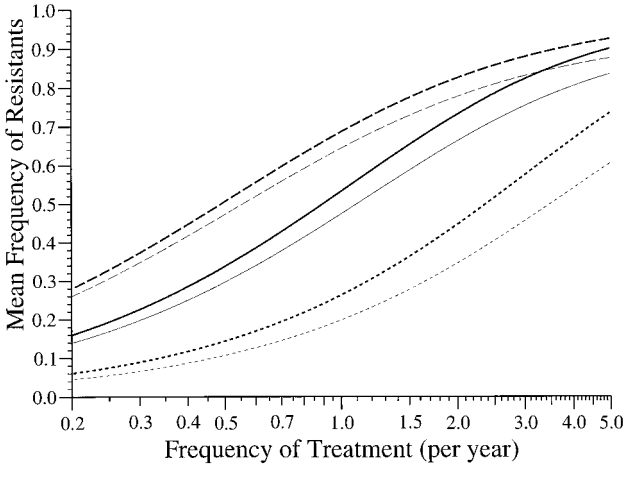

FIG. 5. Mean frequency of resistants in hosts as a function of the frequency of treatment. Migration rate $m = 0.1\%$ per day. Frequency of resistants in the wild $P = 1\%$. Frequency of resistants in treated hosts: wide lines $p^* = 100\%$, thin lines: $p^* = 95\%$. Selection coefficient per generation: dotted lines $s = 5\%$, solid lines $s = 1\%$, dashed lines $s = 0.2\%$.

Figure 6 shows that the level of resistance in the environment has virtually no effect on the equilibrium average level of resistance in hosts. This effect occurs because, provided any host that is treated harbors enough resistant bacteria for antibiotic-mediated selection to work (an assumption of the model), changes in P are likely to have little effect on the calculations. A change in P will merely change one small value of a to another small value. This expectation is confirmed by Fig. 6 which shows that changing P between 0 and 10 % has very little effect on the predictions suggested by the model.

Although the migration of resistants has little effect in this model, the migration of sensitives plays two important roles (Levy, 1997), which are shown in Fig. 7. On the one hand, if the migration rate, m, is comparable with the selection rate, s, then the ratio m/s plays a decisive role in all our equations, beginning with (2.2). As Fig. 7 shows, when m and s are of the same order of magnitude—near the left edge of the picture—the effect of the latter is, to a considerable extent, masked by the effect of the former. However, Fig. 7 also indicates that even small values of m may have a significant effect when p^* is near 100 %.

When m is small it is still the m/s ratio that is relevant, but what is now more important is the tradeoff between m and p^*. Figures 8 and 9 present two ways of examining the interaction between the two parameters. From a strictly practical point of view there is little difference between the two figures. If m is small and p^* is near 100 %, the over all level of resistance will inevitably be high and the antibiotic will have lost much of its effectiveness. From a theoretical point of view it may be of interest to look at the interplay

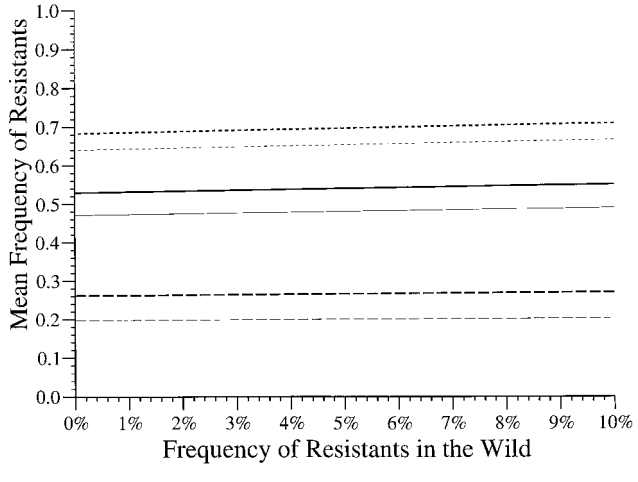

FIG. 6. Mean frequency of resistants in hosts as a function of the the frequency of resistants in the wild. Frequency of treatment $A = 1$ per year. Migration rate $m = 0.1\%$ per day. Frequency of resistants in treated hosts: wide lines $p^* = 100\%$, thin lines: $p^* = 95\%$. Selection coefficient per generation: dashed lines $s = 5\%$, solid lines $s = 1\%$, dotted lines $s = 0.2\%$.

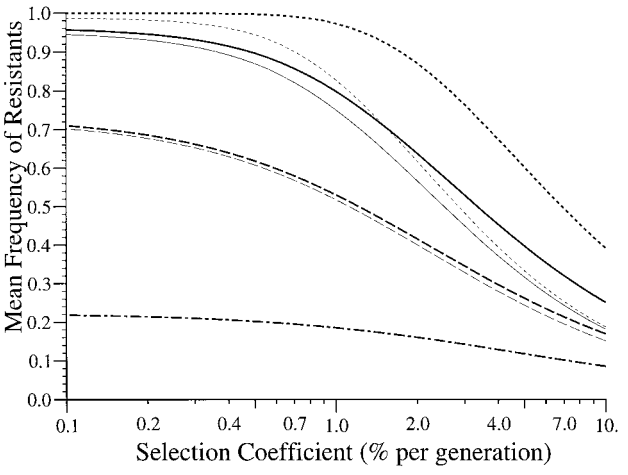

FIG. 7. Mean frequency of resistants in hosts as a function of the selection coefficient. Frequency of treatment $A = 1$ per year. Frequency of resistants in the wild $P = 1\%$. Frequency of resistants in treated hosts: wide lines $p^* = 100\%$, thin lines: $p^* = 99\%$. Migration rate: dot-dash line $m = 10^{-2}$, dashed line $m = 10^{-3}$, solid line $m = 10^{-4}$, dotted line $m = 10^{-6}$. No curve is drawn for the case $m = 10^{-2}$ and $p^* = 99\%$ because it would be indistinguishable from the wide dot–dash line.

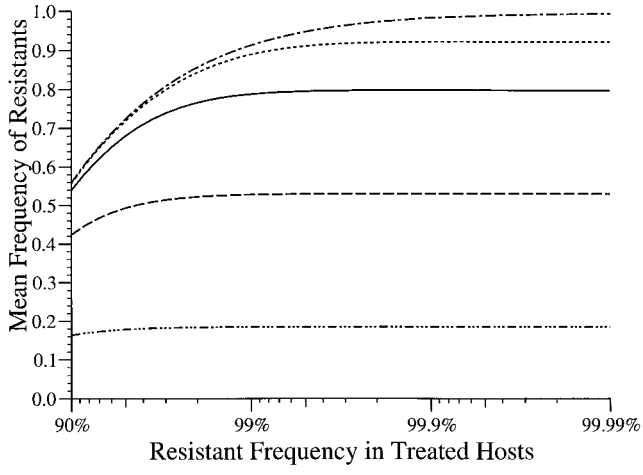

FIG. 9. Mean frequency of resistants in hosts as a function of the frequency of resistants in treated hosts. Frequency of treatment $A = 1$ per year. Selection coefficient per generation: $s = 1\%$. Frequency of resistants in the wild $P = 1\%$. Migration rate, per day: dash-and-dots line $m = 10^{-2}$, dashed line $m = 10^{-3}$, solid line $m = 10^{-4}$, dotted line $m = 10^{-6}$, the dot–dash line shows the behavior when there is no migration at all between hosts and the environment.

in two different ways. In Fig. 8 we show how each value of p^* sets a value of m, below which reducing m makes little difference, while Fig. 9 shows how each m determines a value above which p^* makes little difference.

It is also important to note that unless selection and/or migration rates are quite high, the equilibrium level of resistance may remain quite high, even when treatment frequencies are on the order of 0.1 per capita per year.

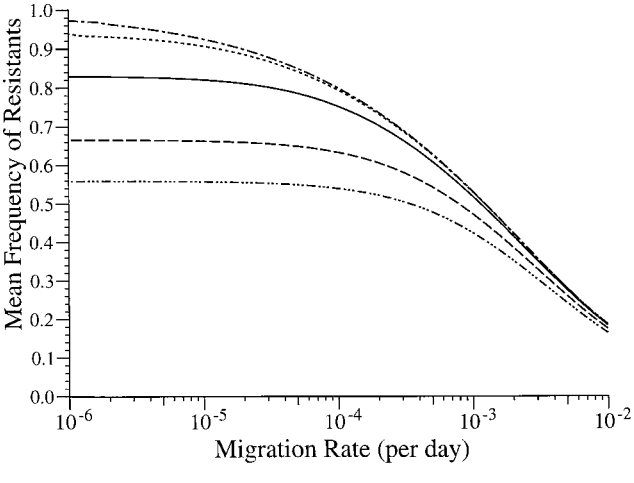

FIG. 8. Mean frequency of resistants in hosts as a function of the the migration rate. Frequency of treatment $A = 1$ per year. Selection coefficient per generation: $s = 1\%$. Frequency of resistants in the wild $P = 1\%$. Frequency of resistants in treated hosts: dash-and-dots line $p^* = 90\%$, dashed line $p^* = 95\%$, solid line $p^* = 99\%$, dotted line $p^* = 99.9\%$, dot–dash line $p^* = 100\%$.

9. GENERAL DISCUSSION AND LIMITATIONS OF THE MODEL

From a biological perspective, it should be pointed out that even if the frequency of resistance declines to low levels, this may not result in a return to the situation prior to the introduction of the antibiotic. The useful life of an antibiotic (the time until resistance is so widespread that the antibiotic is no longer suitable for general use) can be divided into two periods: the period from the first use of the antibiotic until the first appearance of organisms bearing resistance genes for that antibiotic, and the period from the first appearance of those genes to the widespread dissemination of resistant organisms. In some cases, for example vancomycin resistance in enterococci (Arthur *et al.*, 1996), the first period was quite long (on the order of 30 years) but the spread of clinically significant vancomycin resistance has been rapid, making the second period short. In such situations, even if it were possible to drive down the frequency of antibiotic resistance by temporarily reducing antibiotic usage, the return of resistance would likely be much quicker than its initial appearance and spread.

This paper treats each host as independent of every other host; there is no traffic of bacteria between hosts, either directly or through the environment. Biologically, this approximation, which is necessary to enable the analytic treatment here, is reasonable in cases in which

there is little traffic of bacteria from hosts to the environment. An alternate assumption (considered in a simulationstudy, Levin *et al.*, 1997) is that hosts exchange bacteria through a common environmental reservoir. The simplification of ignoring exchange between hosts is likely to have negligible effects on our results. Figure 5, shown above, demonstrates that the immigration of resistant bacteria from the environment makes only tiny differences in the equilibrium reached.

The model also does not take into account possible evolutionary changes in the cost of resistance to the antibiotic, s (Bouma and Lenski, 1988; Schrag and Perrot, 1996). The cost of resistance to antimicrobial agents, such as antibiotics and bacteriophage, can be mitigated by subsequent selection for growth in the presence of that antimicrobial agent, as described above. However, the effects of changes in the selective cost of resistance can be modeled using the framework developed here simply by lowering s.

Another assumption of the model is that treatment only transiently reduces the population of bacteria within a host and that the proportion of resistant bacteria in a host following treatment reaches a fixed level, unrelated to the proportion of resistants in that host before treatment. Together these assumptions reflect the observation that resistant bacteria rapidly repopulate the gut following treatment (Levy *et al.*, 1988; Levin *et al.*, 1997).

Finally, this model considers only resistance to a single antibiotic and ignores the possibility of genetic linkage between resistance determinants to different antibiotics. In fact, many resistance genes are carried on plasmids that carry genes for resistance to other antibiotics. Because of this linked resistance, bacteria "traveling down the sensitivity highway" can be sent back to high frequencies of resistance not only due to the application of the specific antibiotic, but also by application of other antibiotics whose resistance determinants are linked to the antibiotic in question. Linkages between resistance determinants that are under selection will increase the effective rate of treatment above the rate of treatment with any individual antibiotic (Summers *et al.*, 1993; Davis, 1994).

Determinations of the severity of the antibiotic resistance problem and the ability to make recommendations about how to deal with the problem depend critically on an accurate understanding of the population dynamics of sensitive and resistant bacteria (Levy, 1997; Levin *et al.*, 1997). This will require close collaboration between population biologists familiar with mathematical models, microbiologists, epidemiologists and clinical investigators to determine the parameters of these models and test their predictions. Careful studies of some such parameters, such as the fitness cost of resistance, have been and are being conducted. Further studies on the changes in bacterial populations in response to patterns of antibiotic uses both within individual hosts (Levy, 1986) and on a hospital- or community-wide level (McGowan, 1986) are urgently needed.

APPENDIX A: NUMERICAL CALCULATION

The quadratic formula easily provides rough bounds for the larger root of the quadratic in (2.2). Thus

$$\left(1+\frac{m}{s}\right)\left(1-\frac{2ms}{(m+s)^2}P\right) \leqslant b = \frac{m+s+\sqrt{(m+s)^2-4msP}}{2s} \leqslant 1+\frac{m}{s}.$$

So, unless P is large and m is comparable to s, $b \approx 1+m/s$. It is not a good idea to use the quadratic formula to calculate the smaller root because that may involve taking the difference of two nearly equal quantities. It is better to divide the constant term by the larger root. Thus

$$a = \frac{mP}{s}/b \approx \frac{mP}{m+s}.$$

It should now be clear why P, so long as it is not very large, has little effect on the predictions of the model. To a first approximation the fundamental rate constant is

$$\kappa \approx (s+m)\left\{1-\frac{1}{2}\frac{4smP}{(s+m)^2}\right\}.$$

In Section 7 and the computations below

$$p(x) = \frac{a+bu^*e^{-x}}{1+u^*e^{-x}}.$$

First let $y = e^{-Bx}$. Then

$$x = -\frac{\ln y}{B}, \qquad e^{-Bx}\,dx = -\frac{1}{B}\,dy, \qquad \text{and}$$

$$\int_0^{\kappa t} p(x)\,e^{-Bx}\,dx = \frac{1}{B}\int_{y_0}^{1} p(x)\,dy$$

where

$$y_0 = e^{-B\kappa t} = e^{-At}.$$

For efficient numerical calculation of the second integral in (7.1) it may be necessary to introduce an additional parameter. Let $y = e^{-\rho(\kappa t - x)/\kappa\bar{\delta}}$. Then

$$e^{-(\kappa t - x)/\kappa\bar{\delta}} = y^{1/\rho},$$

$$x = \kappa t + \frac{\kappa\bar{\delta}}{\rho}\ln y, \qquad dx = \frac{\kappa\bar{\delta}}{\rho y}\,dy,$$

and

$$\int_0^{\kappa t} p(x)\, e^{-(\kappa t - x)/\kappa\bar{\delta}}\,dx = \frac{\kappa\bar{\delta}}{\rho}\int_{y_0}^{1} p(x)\, y^{1/\rho - 1}\,dy \qquad \text{where} \quad y_0 = e^{-\rho t/\bar{\delta}}.$$

Finally, let $y = e^{-B_0 x}$. Then

$$x = -\frac{\ln y}{B_0}, \qquad e^{-B_0 x}\,dx = -\frac{1}{B_0}\,dy,$$

and

$$\int_{\kappa t}^{\infty} p(x)\, e^{-B_0 x}\,dx = \frac{1}{B_0}\int_0^{y_1} p(x)\,dy$$

where

$$y_1 = e^{-B_0\kappa t} = e^{-A_0 t}.$$

The three integrands can be calculated by a single function provided certain parameters are supplied as global variables. Let

$$I(\alpha, \beta, \gamma;\, y_0,\, y_1) = \int_{y_0}^{y_1} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, y^{\gamma}\,dy \qquad \text{where} \quad x = \alpha + \beta\ln y.$$

Then

$$\int_0^{\kappa t} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-Bx}\,dx = \frac{1}{B}\, I(0,\, -1/B,\, 0;\, e^{-At},\, 1),$$

$$\int_0^{\kappa t} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-(\kappa t - x)/\kappa\bar{\delta}}\,dx = \frac{\kappa\bar{\delta}}{\rho}\, I(\kappa t,\, \kappa\bar{\delta}/\rho,\, 1/\rho - 1;\, e^{-\rho t/\bar{\delta}},\, 1), \qquad \text{and}$$

$$\int_{\kappa t}^{\infty} \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}\, e^{-B_0 x}\,dx = \frac{1}{B_0}\, I(0,\, -1/B_0,\, 0;\, 0,\, e^{-A_0 t}).$$

APPENDIX B: ADJUSTING FOR THE DURATION OF TREATMENT

Figures 4–8, which show the equilibrium value of $\bar{p}$ as a function of the various parameters, were drawn for the case where $\bar{\delta} = 0$. Let $\bar{p}_0$ be the value shown in the graph. Then, according to (4.5) and (4.2), $\hat{\phi}(0) = BH$ and $\hat{\phi}(x) = BHe^{-Bx}$. Hence, according to (5.5) and cancelling the H's:

$$\bar{p}_0 = \int_0^{\infty} p(x)\, Be^{-Bx}\,dx \qquad \text{where} \quad p(x) = \frac{a + bu^* e^{-x}}{1 + u^* e^{-x}}.$$

When $\bar{\delta} \neq 0$, (4.3) and (4.2) imply that $\hat{\phi}(x) = B(H - \hat{\Phi})\, e^{-Bx}$ and hence

$$\bar{p} = H^{-1}\left[\hat{\Phi}p^* + \int_0^{\infty} p(x)\, B(H - \hat{\Phi})\, e^{-Bx}\,dx\right]$$

$$= H^{-1}[\,\hat{\Phi}p^* + (H - \hat{\Phi})\,\bar{p}_0\,] = \bar{p}_0 + \frac{\hat{\Phi}}{H}(p^* - \bar{p}_0)$$

where $\hat{\Phi}$ is given by (4.4).

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