

The transmission dynamics of antibiotic-resistant bacteria: the relationship between resistance in commensal organisms and antibiotic consumption

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SUMMARY

We propose a mathematical model of the transmission dynamics of colonization by commensal bacteria within a human community subject to varying levels of antibiotic use designed to control morbidity induced by pathogenic strains of the normally commensal organisms. Colonization is assumed not to induce morbidity in the majority of cases, and antibiotic use is assumed to be related to the arrival and growth of pathogenic strains that give rise to infections including clinical symptoms of disease. In the absence of antibiotic resistance, the model shows how the pattern of antibiotic prescription and use can eliminate the non-pathogenic commensal strains from the host community if the fraction of people taking antibiotics with a defined efficacy exceeds some critical level. The model is extended to take account of the evolution of antibiotic resistance in the commensal population. We assume resistance may be either plasmid-mediated or conferred by selection of low-level pre-existing mutants, and that resistant organisms may experience reduced reproductive fitness. Invasion of the host community by drug-resistant commensals is possible if certain antibiotic prescribing patterns pertain. We calculate these conditions in terms of the transmission parameter of the organism and the level of antibiotic prescription and use. The model is employed to address the issues of how best to use antibiotics in populations harbouring resistant organisms, and when resistant bacteria will out-compete sensitive strains.

1. INTRODUCTION

The continuing spread of antibiotic resistance in a wide variety of important bacterial pathogens is a cause of concern in many regions of the world (Cohen 1992; Neu 1992; Greenwood 1995). For some widely used antibiotics, such as beta-lactams, the steady rise in the prevalence of resistant strains is linked to increased antibiotic consumption in several countries (Baquero 1996*a*; Finch *et al.* 1996).

More generally, however, the link between antibiotic consumption and the prevalence of resistance to a given drug has been difficult to establish for a variety of reasons. Foremost is the dearth of detailed longitudinal studies that combine measures of the prevalence of resistant strains (with precise definitions of the term resistant) with those on the volume of drug use in a defined setting, community, or country. A second issue of importance concerns the knowledge amongst public health scientists and microbiologists of the patterns of change over time in the frequency of resistance that would be predicted on the basis of an elementary knowledge of the population genetics. For example, under a *constant* selection pressure (i.e. a constant

volume of drug use), the change overtime in the frequency of resistance will be sigmoidal in form with a very slow change following the first appearance of resistant strains, a rapid rise some years later, followed by a slow approach to an equilibrium frequency of resistance whose precise level is determined by many factors, including the magnitude of the constant selective force, the relative fitness of resistant versus sensitive strains, and the biological details of how resistance is conferred and transmitted between organisms.

Empirical associations between antibiotic consumption and the frequency of resistance have been observed in several recent studies, both in clinical settings (McGowan 1983; Møller 1989; Gerding *et al.* 1991; Burman *et al.* 1992; Loulergue *et al.* 1994) and to a lesser extent in the community (Nissinen *et al.* 1995; Arason *et al.* 1996). Several of these studies have provided longitudinal data charting the rise of drug resistance in specific bacteria over time, although estimation of antibiotic consumption has proved to be more difficult to quantify precisely.

At present, few mathematical studies have examined the emergence of antibiotic resistance within frameworks that meld elements of population genetics and transmission dynamics. Massad *et al.* have described a hospital-based epidemiological model which addresses

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questions concerning the co-existence of resistant and drug-sensitive bacterial strains, but the proposed structure does not explicitly link resistance to drug consumption (Massad *et al.* 1993). A variant of this model has been used to show how several antibiotics can be used in a hospital setting to minimize the rate of emergence of multi-drug resistant organisms (Austin & Anderson 1997). Recently, a simple model of the population genetics of antibiotic resistance has been developed by Levin *et al.* which considers the selective pressure imposed by drug treatment on a commensal bacteria (Levin *et al.* 1997). In this model, a fixed number of hosts interact with a pool of bacteria in the environment of these hosts, where antibiotic treatment is prescribed at a defined per capita rate. The model enables a relationship to be defined between drug consumption and the frequency of resistance, and analyses suggest that resistant strains can persist even when resistance carries a fitness cost for the specific levels of drug treatment.

In this paper we define an epidemiological model of the colonization of a host (= human) population by a bacterial species which normally exists as a commensal within the host and does not induce measurable morbidity. Many bacterial species typically exist as commensals in their human hosts, for example *Escherichia coli*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus*, such that many people harbour colonies of the bacteria within defined communities with no overt symptoms of disease. Under circumstances that are, typically, poorly understood, certain strains within these colonies may induce diseases such as otitis media and pneumonia that require antibiotic treatment. Although epidemiological data are very limited at present, it is typically assumed that the frequency of drug resistance in those 'treated' infections reflects the resistance levels pertaining in the commensal population within the host community. Treatment acts to increase their frequency in the commensal populations. Furthermore, if resistance is plasmid-mediated, its presence in commensals may result in the transmission of the attribute to more obligate pathogens (Tenover & McGowan 1996). For this reason, a better understanding of the population genetics and transmission dynamics of resistance trends in commensal organisms under selection by antibiotic treatment is required, to improve the management of drug resistance to widely used antibiotics for the morbidity-inducing bacterial strains and species.

2. THEORETICAL FRAMEWORK

We consider a simple mathematical model in which patients experience colonization by a commensal bacterial species. Colonization may induce some morbidity, although it is assumed that treatment is not required due to an absence of clinical symptoms of infection. Antibiotic treatment is assumed to be used *independently* of colonization status in association with infection by other strains or species that induce morbidity.

Initially, we shall assume that patients may be classified as either susceptible $S(t)$, colonized (infected $I(t)$) or receiving antibiotic treatment $T(t)$, and that resistance is not present within the meta-population of bacteria distributed within the host population. Some patients may be taking antibiotics for other infections, and it is assumed that these individuals are prophylactically protected from colonization whilst they are undergoing treatment. New susceptibles enter the population at a rate $\lambda(t)$ and remain in the population for an average duration of time $1/\mu$ (for day-care centres and nursing homes $1/\mu$ will be measured in terms of months). Susceptibles become colonized at a per capita rate $\beta I(t)$ where β is the transmission parameter (equal to the contact rate multiplied by the probability of colonization per contact) and $I(t)$ denotes the number of colonized individuals. Colonised individuals are assumed to clear the commensal after an average duration of time of $1/f$.

Individuals receive treatment with antibiotics at a rate γ per person per unit time and enter an antibiotic treated class, $T(t)$. They maintain treatment for an average duration of time of $1/g$. Treatment is assumed to clear the commensal colonies of bacteria and protect from further colonization whilst the patient is continuing treatment. Expressing these assumptions as a set of coupled differential equations gives

$$dS/dt = \lambda(t) - (\mu + \gamma)S - \beta IS + gT + fI, \quad (1)$$

$$dT/dt = \gamma(S + I) - (\mu + g)T, \quad (2)$$

$$dI/dt = \beta IS - (\mu + \gamma + f)I. \quad (3)$$

As a simplification, we assume that the total host population is of fixed size. This is a realistic approach when we wish to model the effects of colonization within day-care centres, hospitals and nursing homes, where the number of places, beds or staff are limiting factors. Over the time-scales of interest, a fixed population size is also consistent with many communities in the developed world. Since colonization confers no additional mortality, if the total population is fixed to, say, N , individuals, then $N = S(t) + I(t) + T(t)$ implying that the birth rate $\lambda(t)$ is simply μN . With these assumption the model simplifies to the following two equations and one constraint

$$dX/dt = \gamma(x + y) - (\mu + g)X, \quad (4)$$

$$dy/dt = \beta xy - (\mu + \gamma + f)y, \quad (5)$$

$$1 = x + X + y. \quad (6)$$

The equations are expressed in terms of proportions: $S(t) = x(t)N$, $T(t) = X(t)N$ and $I(t) = y(t)N$, and the transmission parameter β has been rescaled such that $\beta \equiv \beta N$. The influence of antibiotic consumption enters the model in both the prescribing rate γ and the duration of treatment $1/g$. When trying to formulate policies of 'best practice' in terms of minimizing the frequency of antibiotic resistance, both of these parameters are important for the design of appropriate treatment programmes.

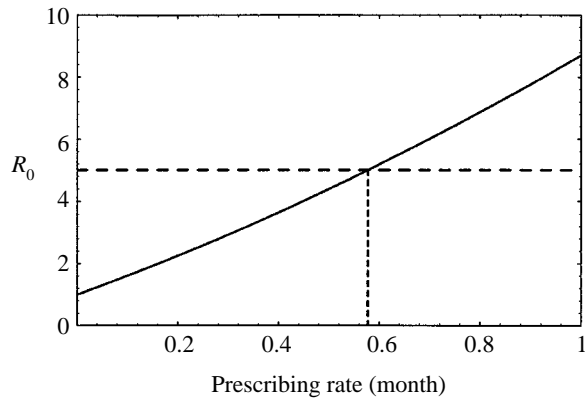


Figure 1. A plot of $\mathcal{R}_0(\gamma)$ as a function of the prescribing rate γ and R_0 (dashed line). Colonization is possible provided that the reproductive ratio R_0 is greater than $\mathcal{R}_0(\gamma)$. This defines a critical prescribing rate γ_c for any R_0 such that when $R_0 = 5$, the commensal will be eradicated if antibiotics are prescribed at a rate of about 0.6 per month. Parameters used are given in table 1.

Table 1. Typical parameter values.

parameter	value	comments
R_0	10	90% of community is colonized w/o antibiotics
μ	1/72 (/month)	six year exposure (e.g. day-care or nursing home)
γ	1/12-1 (/month)	antibiotics prescribed yearly to monthly
f	1/2 (/month)	two month colonization
g	3 (/month)	ten day course of treatment

In this, the most simple of models, the dynamics are governed entirely by the basic reproductive ratio R_0 of the commensal organism. R_0 measures the number of secondary colonizations produced in a naïve host population by a single colonized host (Anderson & May 1991), and is given by

$$R_0 = \frac{\beta}{\mu + f}. \tag{7}$$

For a commensal to become established R_0 must be greater than unity. Every colonization must lead to at least one more colony. After an initial epidemic, the level of colonization will settle to an endemic equilibrium state such that the proportion susceptible is $1/R_0$ and the proportion colonized is $1 - 1/R_0$.

Introducing antibiotics reduces the effective duration of infectiousness since commensals are removed during treatment. Given a constant prescribing rate γ , the proportion p_A taking antibiotics at any time is simply

$$p_A = \frac{\gamma}{\gamma + g + \mu}. \tag{8}$$

Antibiotic consumption also protects people from colonization over the duration of treatment. We shall assume that protection is total, and hence only a proportion $1 - p_A$ of individuals are either susceptible

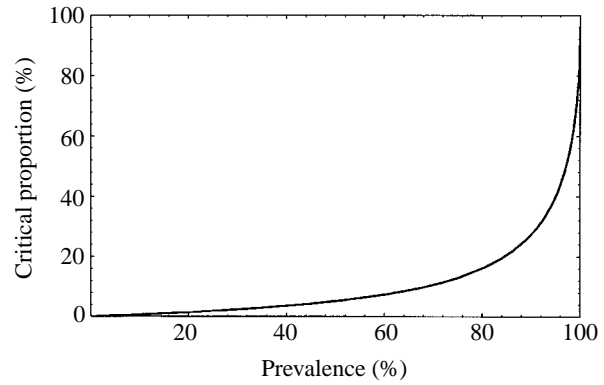


Figure 2. The critical proportion of people who must take antibiotics to eradicate colonization, as a function of prevalence of carriage prior to treatment. Highly prevalent bacteria require sustained and intensive antibiotic therapy if they are to be eradicated. Increasing duration of carriage ($1/f$) or reducing duration of antibiotic therapy ($1/g$) makes eradication more difficult.

or colonized (i.e. $x + y = 1 - p_A$). Therefore, at endemic equilibrium

$$x^* = \frac{1}{R_0} \left(1 + \frac{\gamma}{\mu + f} \right), \quad y^* = 1 - p_A - x^*, \quad X^* = p_A, \tag{9}$$

where * denotes an endemic state. For a commensal to become established within a community requires that $y^* \geq 0$, or equivalently that

$$R_0 > \mathcal{R}_0(\gamma), \tag{10}$$

where $\mathcal{R}_0(\gamma)$ is a factor describing how R_0 is reduced by treatment and takes the form

$$\mathcal{R}_0(\gamma) = \left(1 + \frac{\gamma}{\mu + f} \right) \left(1 + \frac{\gamma}{\mu + g} \right). \tag{11}$$

Figure 1 shows the variation of $\mathcal{R}_0(\gamma)$ as a function of the prescribing rate γ . We assume that in the absence of treatment $R_0 > 1$ (i.e. the commensal is naturally present). Since $\mathcal{R}_0(\gamma)$ is an increasing function of γ , eventually the prescribing rate reaches a critical rate γ_c above which the inequality of equation (10) cannot be satisfied. At this point, antibiotic prescribing has removed sufficient individuals from the susceptible class so that the commensal will be eradicated from the community. Solving the inequality gives the critical prescribing rate

$$\gamma_c = \frac{(f' + g')}{2} \left\{ \sqrt{1 + \frac{4f'g'(R_0 - 1)}{(f' + g')^2}} - 1 \right\}, \tag{12}$$

where $f' = f + \mu$ and $g' = g + \mu$. Substituting the critical value γ_c into our earlier expression for the proportion taking antibiotics gives a critical proportion, $p_A(\gamma_c)$, necessary to eradicate a commensal bacterial organism. Figure 2 shows the proportion who must take antibiotics for eradication as a function of the prevalence of colonization (= the carrier state) in the absence of treatment ($1 - 1/R_0$). As in the case of vaccination, highly transmissible commensals require

a sustained effort before they can be eradicated by community-based antibiotic treatment.

3. ANTIBIOTIC RESISTANCE

Drug resistance may be conveyed in bacteria by a number of biological mechanisms, such as mutation and the exchange of genetic information in the form of plasmids. In an epidemiological framework, however, it is the role antibiotic consumption plays in the onset and propagation of resistance within the environment that is the key issue. We assume the presence of a second drug-resistant strain circulating within the community. With two strains the model becomes more complex. For simplicity, we shall assume that individuals can only be colonized with a single strain, and that if colonized by resistant organisms, then antibiotics may either have no effect or select for pre-existing resistant mutants. Furthermore, we assume that hosts colonized with resistant bacteria can transmit plasmids which confer resistance to sensitively colonized hosts. These assumptions require two additional classes: (i) hosts that are colonized by the resistant strain (z) and (ii) hosts that are colonized by the resistant strain *and* taking antibiotics ($Z(t)$).

Figure 3 shows a representation of the expanded model. With the same constant population size as in the simple model, the full equations are

$$dX/dt = \gamma x + \gamma(1 - \sigma)y - (\mu + g)X - \beta' XZ + f'Z, \tag{13}$$

$$dy/dt = \beta xy - \xi Zy - (\mu + f + \gamma)y, \tag{14}$$

$$dz/dt = \beta' xZ + \xi Zy - (\mu + f' + \gamma)z + gZ, \tag{15}$$

$$dZ/dt = \beta' XZ + \sigma\gamma y + \gamma z - (\mu + f' + g)Z, \tag{16}$$

$$1 = x + X + y + Z, \tag{17}$$

$$Z = z + Z. \tag{18}$$

All parameters have the same definitions as in the simple model. Resistant strains have their own transmission parameter, β' , and duration of colonization, $1/f'$, which may or may not be the same as sensitive strains. Furthermore, we assume a proportion σ of individuals who are sensitively colonized will select pre-existing antibiotic-resistant mutants once they undergo treatment. Plasmid transfer is measured by the transmission parameter, ξ which is analogous to β' , equal to the contact rate between hosts multiplied by the probability that the plasmid is transferred between hosts (c.f. β' which is measured by the contact rate multiplied by the probability of colonization). If during a single contact, colonization and plasmid transfer are equally likely, then ξ is equal to β' . In general, we might expect that more plasmid-bearing organisms are required to transfer resistance to sensitively colonized hosts compared to the colonization of commensal-free hosts (i.e. $\beta' > \xi$).

When antibiotics were first introduced to treat bacterial infections the bacterial populations were

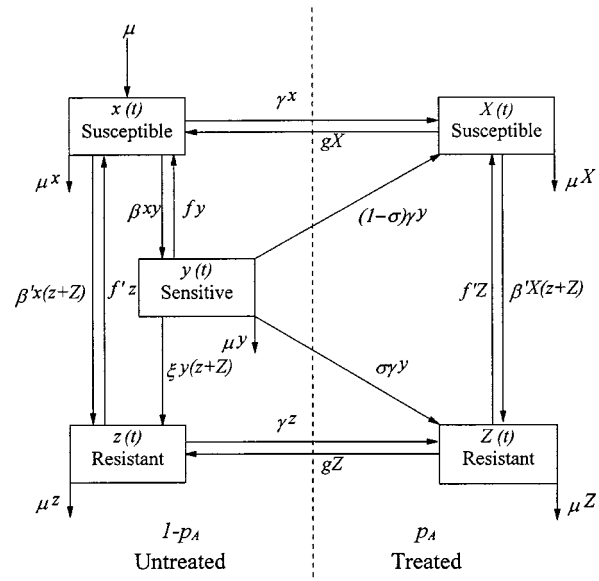


Figure 3. Model of antibiotic therapy and colonization incorporating drug-sensitive and resistant strains. Individuals are born into an antibiotic-free susceptible class (x) and maybe colonized by either sensitive (y) or resistant bacteria (z and Z). In addition, individuals are prescribed antibiotics at a rate γ and enter either a treated susceptible class (X) or treated resistant class (Z) depending upon their colonization status. Resistance can be conferred by either (i) selection of resistant mutants during treatment ($y \rightarrow Z$) or (ii) plasmid transfer from resistantly colonized hosts ($y \rightarrow z$). Following the introduction of treatment, a proportion $p_A = X(t) + Z(t)$ are being treated with antibiotics at all times.

thought to be totally susceptible. One explanation for this is that in the absence of drug selection pressures, drug-resistant organisms experience some form of fitness cost (Frank 1996). In this framework, we introduce a fitness cost in the form of a reduced basic reproductive ratio for the resistant strain, i.e.

$$R'_0 = \frac{\beta'}{\mu + f'} \leq R_0. \tag{19}$$

Where two strains are competing for resources (in this case hosts to colonize) classical ecological theory predicts that the strain with the highest R_0 will out-compete the other strains. Naïvely, we might therefore predict that in the absence of selection, the resistant strain will be eliminated from the community. Antibiotic treatment can either upset the balance in reproductive ratios such that the resistant strain gains the advantage, or it can create a niche of treated hosts who can be resistantly colonized overcoming the competition. Introducing mutation and plasmid transfer can further overcome the competition between strains and stabilize coexistence between drug-sensitive and drug-resistant strains which otherwise might not be possible.

4. DYNAMICS

The dynamics of the full model are much more complex than the simple framework without resistance.

In the absence of any drug-resistant strains ($\mathcal{Z} = 0$) the dynamics remain unchanged from the simple model (equations (4)–(11)). The overall dynamics are determined by the basic reproductive ratios R_0 and R'_0 , which we shall assume are greater than unity (otherwise the commensal will never become established). Including resistance allows for the possibility of invasion by a resistant strain, and the full model framework allows us to address issues of whether resistance will enter a community and whether once present it will come to dominate over sensitive strains.

(a) No colonization

$$Q_0 \equiv (1 - p_A A, 0, 0, 0)$$

We know from the simple model that a community can withstand invasion by drug-sensitive commensals provided that the antibiotic prescribing rate is greater than the critical rate γ_c (equation (12)). Furthermore, in the absence of drug-sensitive colonization, everyone remains susceptible to drug-resistant strains, regardless of antibiotic treatment. Provided that the resistant strains can be independently transmitted (i.e. $R'_0 > 1$), then the community will become colonized. Questions remain, however, about whether a community which is subject to entirely resistant colonization can be replaced by a sensitive commensal, and what changes in treatment patterns are required to achieve this.

(b) Sensitive colonization

$$Q_1 \equiv (x^*, y^*, 0, 0)$$

Q_1 is the same endemic state as the simple model prior to the introduction of resistance, and is given by equation (9). We have already shown that increased prescribing will lead to the eventual removal of sensitive colonization once the prescribing rate exceeds γ_c . Whether a resistant strain will invade a community depends upon the exact assumptions regarding the transmission of drug resistance. Ignoring the two resistance mechanisms (mutation and plasmid transfer), an uncolonized community will be susceptible to drug-resistant commensals provided that a sufficient proportion of the community remain susceptible to colonization (i.e. in classes x and X). Equivalently the reproductive ratio for the resistant strains must satisfy

$$R'_0 > R_0^s, \tag{20}$$

where R_0^s is the critical reproductive ratio necessary for drug-resistant commensals to invade a drug-sensitive colonized community, and is given by

$$R_0^s = \frac{1}{1 - y^*}. \tag{21}$$

Since R_0^s is greater than unity, colonization of a community by drug-sensitive commensals can protect a community from invasion by drug-resistant commensals provided that the level of antibiotic consumption remains below a critical threshold.

If antibiotic treatment selects for pre-existing drug-resistant mutants ($\sigma \neq 0$), then the very action of introducing treatment will *always* give rise to resistant colonization of some members of a community, and

hence coexistence. Plasmid-mediated drug resistance allows uncolonized hosts to acquire resistance by direct transmission, and drug-sensitive colonized hosts by the acquisition of genetic information from other resistantly colonized hosts. There is therefore an increase in the proportion of hosts that remain susceptible to colonization by drug-resistant strains, such that the critical reproductive ratio R_0^s is reduced to

$$R_0^s = \frac{1 - R''_0 y^*}{1 - y^*}. \tag{22}$$

R''_0 is the reproductive ratio of the *plasmid* which mediates resistance and is an independent measure of resistance transmission. In common with the reproductive ratio R'_0 , the plasmid reproductive ratio is of the form

$$R''_0 = \frac{\xi}{\mu + f'}, \tag{23}$$

and can be defined as the average number of secondary hosts ‘infected’ with the plasmid by a single plasmid-bearing host when introduced to a wholly colonized plasmid-free community. If the plasmid is truly independently transmissible (as might be the case for bacterial viruses), then we would expect R''_0 to be greater than one. If, however, $R''_0 y^* > 1$ then equation (22) implies that drug resistance will *always* become established within a community due to plasmid-mediated spread rather than direct transmission of drug-resistant bacteria, irrespective of issues of transmission fitness cost. Introducing plasmid transfer has in effect decoupled the transmission of bacteria from the population genetics of plasmid transfer. How plasmids can become stabilized within a community will be dealt with in greater detail elsewhere (Austin & Anderson 1997*b*).

(c) Resistant colonization

$$Q_2 \equiv (x^*, X^*, 0, z^*, \zeta^*)$$

If drug-resistant bacteria are introduced into an uncolonized community, or have a transmission fitness advantage (which may be induced by antibiotic treatment), then the system will evolve towards fixation (Q_2). Since we have assumed that antibiotic prescribing is independent of colonization status, the proportion colonized by drug-resistant commensals will be $1 - 1/R'_0$, and the proportion treated with antibiotics will be p_A . Therefore, once drug resistance has reached fixation, the endemic state Q_2 will be given by

$$\begin{aligned} x^* &= \frac{(1 - p_A)}{\chi R_0}, & X^* &= \frac{p_A}{\chi R_0}, \\ z^* &= (1 - p_A) \left(1 - \frac{1}{\chi R_0}\right), & \zeta^* &= p_A \left(1 - \frac{1}{\chi R_0}\right). \end{aligned} \tag{24}$$

Drug-resistant commensals will persist provided that the drug-sensitive strain cannot reinvade. Neglecting mutation and plasmid-mediated resistance mechanisms, the drug-resistant strain will cease to

remain endemic provided that the reproductive ratio of the drug-sensitive invading strain satisfies

$$R_0 > R'_0 \mathcal{R}_0(\gamma). \tag{25}$$

Comparing this expression with equation (11) we see that once a drug-resistant commensal has reached fixation, it will be R'_0 times harder for it to be disturbed by a drug-sensitive strain. This is a further example of how prior colonization by one form of commensal can protect a community against other forms. If the drug-sensitive strain has only a slight transmission fitness advantage over the resistant strain, reintroducing the drug-sensitive strain once fixation has been reached may require a reduction in $\mathcal{R}_0(\gamma)$ via a reduced prescribing rate, γ . Conversely, if the drug-resistant strain has a fitness advantage ($R'_0 > R_0$), then the sensitive strain cannot be reintroduced.

Selecting pre-existing drug-resistant mutants by antibiotic treatment has little effect on levels of drug-resistance once fixation has been reached. However, the action of plasmid-mediated drug-resistance will serve to make the fixation of drug resistance *more* stable because it provides an independent way in which drug-sensitive commensals can be replaced by drug-resistant ones (see Appendix 1).

(d) Coexistence

$$Q_3 \equiv (x^*, X^*, y^*, z^*, \zeta^*)$$

In many instances where drug resistance has been identified, its identification has led neither to eradication (Q_1) nor fixation (Q_2), but to a state of coexistence where both drug-sensitive and drug-resistant commensals circulate within a host community. Exact calculation of the full endemic equilibrium is given in Appendix 1. Establishing the stability of coexistence is very difficult, however we can gain an intuitive idea, given that we require that *both* singly colonized endemic states be unstable to invasion (figure 4). In the absence of mutation (which can always stabilize coexistence) and plasmid transfer, stable coexistence of sensitive and resistant commensals requires that the reproductive ratio for the drug-resistant strain lies in the range

$$R_0^s < R'_0 < R_0^r, \tag{26}$$

where R_0^r is given by $R_0/\mathcal{R}_0(\gamma)$ (equation (25)), and $R'_0 < R_0$. Coexistence will therefore only be possible when $R_0^s < R'_0$. Conversely, if $R_0^s > R'_0$, colonization imparts additional stability to invasion and coexistence will not be possible. Figure 5 shows how both R_0^s and R_0^r vary as functions of prescribing rate and the corresponding region of coexistence. Coexistence depends upon the size of the niche created by treated hosts. Where a high proportion of the population are being treated with antibiotics (such as in hospitals) we would expect the duration of the stay to be approximately equal to the time between treatments (i.e. $\gamma \simeq \mu$). This makes the coexistence region larger (all other parameters remaining equal) suggesting that coexistence between drug-sensitive and resistant strains will be more likely in clinical settings compared to areas with

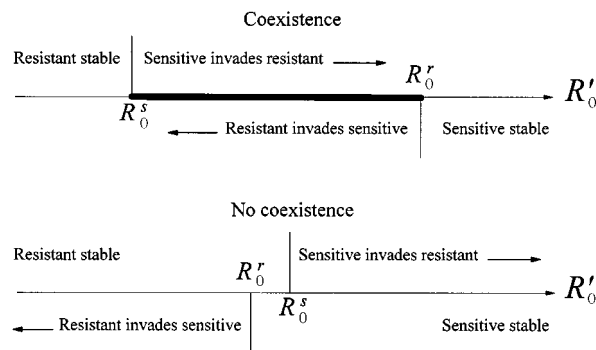


Figure 4. Representation of the coexistence criteria. Coexistence requires $R_0^s < R'_0 < R_0^r$ which is only possible when $R'_0 > R_0^s$. Non-overlapping regions of stability allow coexistence, overlapping regions impart extra stability to whichever strain is present.

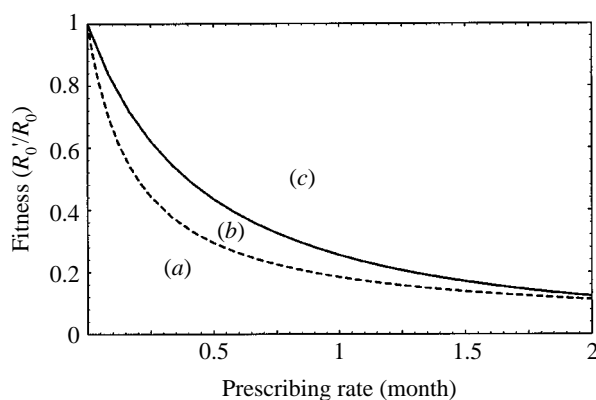


Figure 5. Endemic regions; sensitive (a), resistant (c) and coexisting (b) for different prescribing rates and transmission fitness cost (defined as R'_0/R_0). Stability requires $R_0^s < R'_0 < R_0^r$ (solid line) which have all been scaled by R_0 . Parameters used are given in table 1.

lower antibiotic usage, such as day-care centres and nursing homes.

Mutation imparts a natural coexistence to the system which can overcome all aspects of competition for susceptible hosts provided that antibiotic treatment is maintained (typically $Z^* \simeq \sigma y^*$). If the basic reproductive ratio R'_0 lies below R_0^r then drug resistance will not reach fixation, and the level of resistance will be determined by both the antibiotic prescribing rate and the proportion of treated hosts that select drug-resistant commensals. Plasmid-mediated resistance again requires $R_0^s < R'_0 < R_0^r$, although both R_0^s and R_0^r are reduced such that if the plasmid can be independently transmitted ($R_0^r > 1$) then the reproductive ratio for the drug-resistant strain need not be greater than unity (see Appendix 1).

The emergence of antibiotic resistance may occur gradually over time even under conditions of a constant antibiotic selection pressure. Selection of resistance can take place in the absence of changes in prescribing practice. In figure 6, we show how a highly prevalent commensal ($R_0 = 10$) can successfully be selected for by intense antibiotic treatment within a community. In this example, the use of antibiotics prior to the introduction of resistance has reduced the prevalence from an expected 90% to 77%. Antibiotics are prescribed

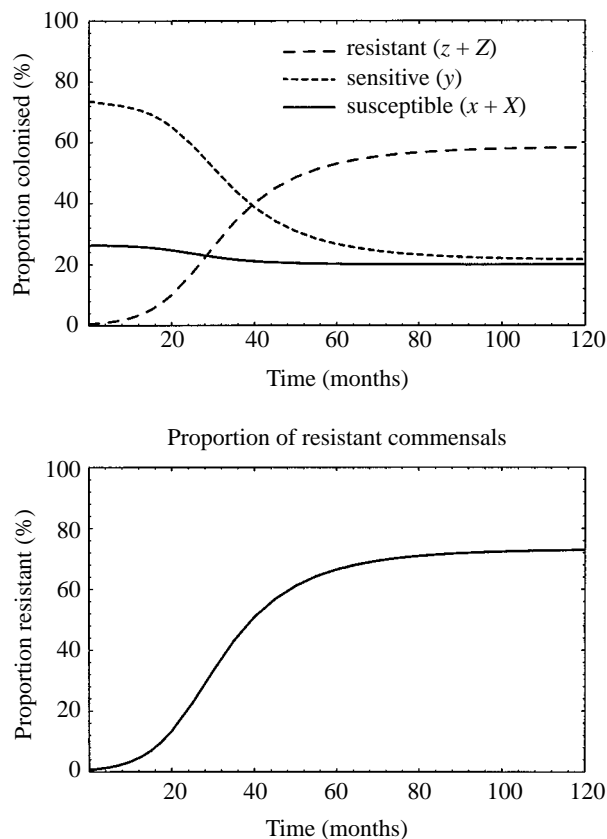


Figure 6. Emergence of antibiotic resistance in a community following ten years of *constant* intensive antibiotic consumption. Overall prevalence remains approximately constant, however, resistance increases to 72%. Antibiotics are prescribed at a rate of once every three months ($\gamma = 0.33$ per month), other parameters are given in table 1. Resistant bacteria are assumed to have a transmission fitness cost of 50% such that $R'_0 = 0.5R_0$, and are therefore half as transmissible as sensitive bacteria. No mutation or plasmid transfer is included, coexistence occurs as a result of niche colonization of treated hosts by drug-resistant strains.

at a constant rate of once every three months for ten days ($p_A \simeq 10\%$), which would not be unusual in the close confines of a nursing home or day-care centre. After introduction, resistance takes about five years to reach an equilibrium frequency of 72% of those colonized. Increasing R'_0 for the resistant strain will increase both the proportion of resistant cases (eventually leading to fixation), and the rate of emergence.

When antibiotic resistance is introduced into a community (or develops through mutation or plasmid transfer), whether it will subside, stabilize, or reach fixation depends both on the relative transmission fitness of the resistant strain (R'_0/R_0) and the antibiotic prescribing rate (γ). Figure 7 shows the endemic proportion of hosts colonized with resistant bacteria,

$$p_R = \frac{Z^*}{y^* + Z^*}, \quad (27)$$

as a function of the prescribing rate. For simplicity, we have ignored mutation and plasmid transfer, and in doing so observe a threshold prescribing rate above which resistance becomes established, leading to

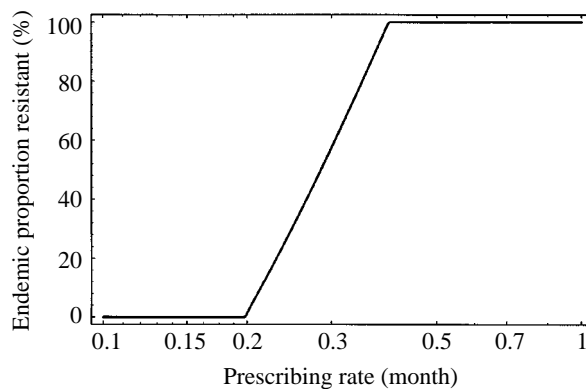


Figure 7. Endemic proportion p_R colonized with antibiotic-resistant commensals as a function of the prescribing rate γ for the simple model with a 50% transmission fitness cost for resistant commensals. Parameters used are given in table 1 and no mutation of plasmid transfer is included. Increasing the prescribing rate above a threshold of 0.2 per month leads to the emergence of resistance which reaches fixation. Increasing R_0 shifts the curve to higher prescribing rates and makes the transition more rapid. Increasing the transmission fitness reduces the threshold prescribing rate. Highly prevalent commensals which experience a large transmission fitness cost for resistance can withstand antibiotic selection much more effectively than less prevalent ones.

fixation when antibiotics are prescribed extensively. Increasing R_0 will lead to an increased threshold prescribing rate and a much steeper transition to fixation. Increasing R'_0 (i.e. increasing transmission fitness) reduces the threshold. Commensals which are more prevalent, and therefore have greater transmission potential, or experience a high transmission fitness cost, can withstand higher prescribing rates without being eliminated from the host population, primarily because they have colonized extensively, reducing the niche available for the drug-resistant strains.

Using the endemic proportion that are carriers of *antibiotic resistant strains* as a measure, we can look at the effect of using different treatment profiles. For example, what are the relative effects on resistance of short intensive treatments administered to most infected people compared with longer treatments given to fewer individuals? Furthermore, what effect does transmissibility (R_0) have on resistance for a given level of antibiotic consumption?

Figure 8 addresses these questions in the absence of mutation and plasmid-mediated resistance mechanisms. In Figure 8a, we show the variation of p_R with prescribing rate γ and treatment duration $1/g$ and fixed R_0 ($R_0 = 10$ is equivalent to nine persons in ten being colonized). There is a clear trade-off between prescribing rate and duration of treatment. As expected, when resistance is present, it is minimized using shorter treatments for a given prescribing rate. Figure 8b shows the variation of p_R with prevalence and the proportion taking antibiotics, p_A . Where colonization is extensive (high R_0 values), antibiotics can be used with less risk of resistance. However, when colonization is at low levels (i.e. low R_0 values) the appearance and establishment of resistance is a much greater problem.

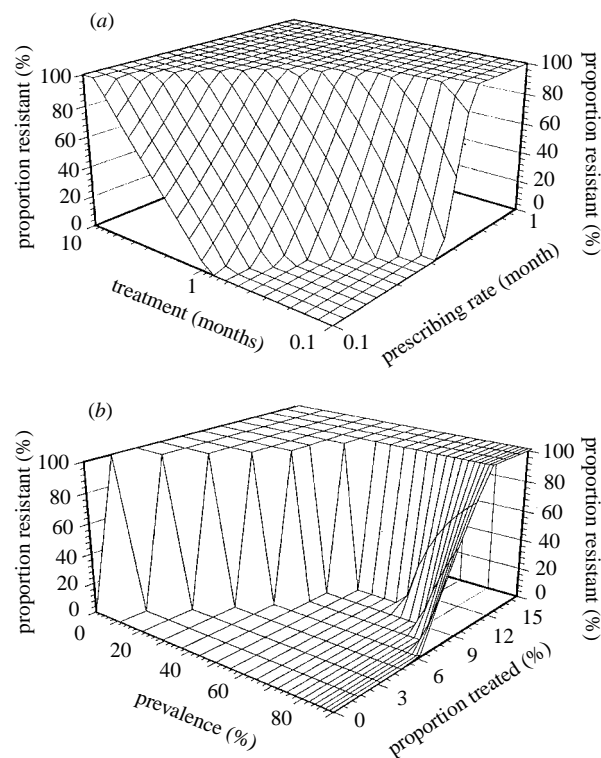


Figure 8. Endemic proportion p_R colonized with antibiotic-resistant commensals in the simple model without mutation or plasmid transfer as functions of (a) prescribing rate and duration of treatment, and (b) prevalence and proportion taking antibiotics. Parameters used are given in table 1 and resistant strains have a 50% transmission fitness cost. There is a trade-off between prescribing rate and treatment duration such that short courses can be given more frequently than long courses. Highly prevalent commensals provide a form of herd immunity to resistance so that a greater proportion of people can take antibiotics for a given level of resistance.

5. DISCUSSION

We have described a simple epidemiological model of the colonization of a population by commensal bacteria. By introducing antibiotic consumption into the model and assuming that individuals receive treatment for infections independent of their commensal flora, we are able to study the relationship between antibiotic consumption and colonization. A commensal is able to colonize a community if its basic reproductive ratio R_0 , defined as the number of secondary individuals who are colonized when a single carrier enters a naïve community, is greater than unity. Since the endemic prevalence is simply $1 - 1/R_0$, estimates suggest R_0 values of approximately 1–10 for many of the common commensal bacteria of human communities. We assume that when an individual is prescribed antibiotics, both the pathogen and any drug-sensitive commensals are cleared. The implication from this assumption is that those who are taking antibiotics are protected from colonization by drug-sensitive commensals during the course of treatment. Therefore, if antibiotic consumption is sufficiently high, a commensal can be eradicated from a population when the prescribing rate γ exceeds some critical level (or, equivalently, when a critical proportion

are taking antibiotics at any one time). This result may be of practical significance in infection control in hospitals where antibiotics are frequently administered prophylactically.

We have assumed that drug-resistant implies wholly resistant, and therefore, individuals who are taking antibiotics remain susceptible to colonization by drug-resistant commensals. This can create a niche for resistant strains, although the trait of resistance may be subject to some fitness cost. We examine two mechanisms by which resistance can be transferred between hosts, namely the selection of pre-existing mutants during treatment and the transfer of genetic material via plasmids to sensitively colonized hosts. The selection of pre-existing mutants will always give rise to resistance once new drugs are introduced, and lead to fixation given sufficiently high drug usage. Plasmid-mediated resistance provides the opportunity for resistance to be conveyed independently, thereby increasing the proportion of hosts that are susceptible to drug resistance. We have shown that if the plasmid is sufficiently transmissible, then the trait of drug resistance can be maintained solely by plasmid transfer, even in the absence of drug selection pressures. This provides one explanation of the very rapid onset of resistance sometimes seen when new drugs are introduced. If the plasmid is not sufficiently transmissible in its own right ($R_0'' < 1$), then we predict that if antibiotic consumption remains below a threshold level (either as the prescribing rate or the proportion taking antibiotics), then a resistant strain will not be able to establish within the host community.

The exact nature of the fitness cost for most drug-resistant bacteria is unknown with respect to impact on transmission success. However, reduced transmissibility is the most probable effect, although in some cases resistance may carry no costs at all. Where there is no fitness cost we predict that under antibiotic selection pressure drug-resistant commensals will reach fixation and completely replace sensitive commensals. Furthermore, there will be no opportunity to return to drug sensitivity. If resistance is associated with a fitness cost (perhaps the plasmid codes for other traits which reduce transmission), then selection pressures may under some prescribing practices lead either to no resistance being present, or stable coexistence between sensitive and resistant strains.

The existence of a threshold antibiotic prescribing rate, both to eradicate a commensal and to prevent the emergence of resistance, suggests that maintaining a population free of a single resistance mechanism can be achieved by restricting or controlling the community-wide antibiotic consumption rate. Once antibiotic resistance has become established, the most pressing questions are those concerning its control and, perhaps, its eradication. Our results suggest that once resistance has reached fixation, a return to coexisting or drug-sensitive colonizations is much harder to achieve and will require changes in prescribing practice. Some surveys of resistant organisms (albeit typically based on samples from clinical settings) have shown coexistence of drug-resistant and sensitive strains (Nissinen *et al.* 1995). A complete cessation of antibiotic use (or a switch to an

antibiotic with a different resistance mechanism) will generally lead to the gradual, though often not complete, removal of a drug-resistant commensal. The rate of removal will, however, typically be much slower than that of emergence and, if not completely removed, drug-resistant commensals will ascend once treatment is restarted (Levin *et al.* 1997).

The model presented here makes few assumptions other than commensal colonization takes place and may not induce morbidity, and antibiotic consumption is independent of colonization. To apply the model to specific cases of the emergence of resistance in hospital or other settings, we require estimates of prevalence (R_0), duration of colonization ($1/f$), antibiotic prescribing rate (γ) and duration of treatment ($1/g$). Although exact data regarding prevalence and duration of colonization are scarce, the increasing awareness of the threat of resistance has given rise to greater numbers of studies in recent years. Antibiotic consumption data are now being made available through marketing databases worldwide (Baquero 1996*b*) which measure consumption as defined daily doses (DDDs). The DDD gives an estimate of the proportion of people taking antibiotics, although this may not be broken down into epidemiologically relevant classes (e.g. children, adults less than 65 years old and adults more than 65 years old). Applying this model, we show in another paper how the rise in *Moraxella catarrhalis* in Finnish children can be accurately predicted given the necessary resistance and consumption data (Austin *et al.* 1998).

A return to the days of fully antibiotic-susceptible pathogens and the eradication of drug resistance is of course unlikely. Certainly reductions in resistance levels are possible and have been seen in clinical settings when antibiotic prescribing patterns are changed (i.e. different compounds and different levels of consumption) (Barber *et al.* 1960). Within the community, however, the options available are less easily implemented without government legislation to provide options on the type and volume of drug use in whole communities or large aggregations of people. Patients with community-acquired infections have expectations of antibiotic therapy which have in the past been met with effective treatment. The blanket prescribing policies of the past will cease to maintain that effectiveness in the future.

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APPENDIX 1

The stability of the endemic colonizations Q_1 , Q_2 and Q_3 can be calculated for the full model, including mutation and plasmid transfer. Since antibiotic prescribing is assumed to be independent of colonization status, $X + Z$ remains a fixed proportion p_A of the

total population. The full model is given by equations (13)–(18).

Combining dz/dt and dZ/dt gives

$$dZ/dt = \beta'(1 - y - Z)Z + \xi Z y - (\mu + f')Z + \sigma \gamma y. \tag{28}$$

Setting this equal to zero gives the endemic relationship

$$y^*(Z^*) = \frac{Z^*(R'_0(1 - Z^*) - 1)}{(R'_0 - R''_0)Z^* - \sigma\gamma/(\mu + f')}. \tag{29}$$

$dy/dt = 0$ implies that x^* is given by

$$x^*(Z^*) = \frac{1}{R_0} \left(1 + \frac{\gamma}{\mu + f} \right) + \frac{\xi Z^*}{\beta}, \tag{30}$$

and we know that

$$z^*(Z^*) = p_A - x^*(Z^*) - y^*(Z^*). \tag{31}$$

Substituting these three relationships into $dz/dt = 0$ gives the final equation

$$0 = \left\{ \frac{1}{R_0} \left(1 + \frac{\gamma}{\mu + f} \right) + \frac{\xi Z^*}{\beta} \right\} (\beta' Z^* + (\mu + f' + \gamma + g)) + \left\{ \frac{Z^*(R'_0(1 - Z^*) - 1)}{(R'_0 - R''_0)Z^* - \sigma\gamma/(\mu + f')} \right\} (\xi Z^* + (\mu + f' + \gamma + g)) + g Z^* - (1 - p_A)(\mu + f' + \gamma + g). \tag{32}$$

Coexistence requires one positive real root, Z^* , for this cubic equation. Setting either (i) $\xi = 0$ (no plasmid transfer) or (ii) $\sigma = 0$ (no mutation) after cancellation, reduces the cubic to a quadratic equation. Coexistence requires the existence of one positive real root Z^* . Writing equation (32) in the form $A(Z^2) + BZ + C = 0$ shows that both $\xi = 0$ and $\sigma = 0$, the factor A is always negative requiring that C be positive.

(i) Selection of pre-existing mutants will always give one positive real root Z^* with coexisting drug-sensitive and resistant strains provided

$$R_0 > \mathcal{R}_0(\gamma), \tag{33}$$

implying that when the prescribing rate does not eradicate drug-sensitive commensals, coexistence will always be stable. Conversely, once fixation has been reached (Q_2 , $y^* = 0$), then drug-sensitive commensals can only be reintroduced when $dy/dt > 0$, implying that

$$R_0 > R'_0 \mathcal{R}_0(\gamma), \tag{34}$$

making reintroduction *harder* than in uncolonized populations.

(ii) Plasmid transfer can stabilize coexistence with one positive real root, Z^* , provided

$$R_0 > \mathcal{R}_0(\gamma) \left(\frac{R'_0 - R''_0}{1 - R''_0} \right). \tag{35}$$

This is always true when the plasmid can be transmitted independently from host to host ($R''_0 > 1$), but need not be the case when the drug-resistant strain is

more transmissible than the plasmid ($R'_0 > R''_0$). The stability of fixation (Q_2) is again established by requiring that $dy/dt > 0$, and implies that a drug-sensitive commensal can be reintroduced into a resistantly colonized host population when

$$R_0 > R'_0 \mathcal{R}_0(\gamma) \left(1 + \frac{\xi(\mu + g)}{(\mu + f)(\mu + \gamma + g)} \left(1 - \frac{1}{R'_0} \right) \right). \quad (36)$$

Again this is greater than is required for introduction to an uncolonized population, suggesting that once fixation has been reached, it will be difficult to return to drug-sensitive colonization.

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