PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models

D. J. Austin and R. M. Anderson

Phil. Trans. R. Soc. Lond. B 1999 **354**, 721-738
doi: 10.1098/rstb.1999.0425

THE ROYAL SOCIETY

Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models

D. J. Austin and R. M. Anderson

Wellcome Trust Centre for the Epidemiology of Infectious Diseases, University of Oxford, South Parks Road, Oxford OX1 3PS, UK (daren.austin@zoology.ox.ac.uk)

The emergence of antibiotic resistance in a wide variety of important pathogens of humans presents a worldwide threat to public health. This paper describes recent work on the use of mathematical models of the emergence and spread of resistance bacteria, on scales ranging from within the patient, in hospitals and within communities of people. Model development starts within the treated patient, and pharmacokinetic and pharmacodynamic principles are melded within a framework that mirrors the interaction between bacterial population growth, drug treatment and the immunological responses targeted at the pathogen. The model helps identify areas in which more precise information is needed, particularly in the context of how drugs influence pathogen birth and death rates (pharmacodynamics). The next area addressed is the spread of multiply drug-resistant bacteria in hospital settings. Models of the transmission dynamics of the pathogen provide a framework for assessing the relative merits of different forms of intervention, and provide criteria for control or eradication. The model is applied to the spread of vancomycin-resistant enterococci in an intensive care setting. This model framework is generalized to consider the spread of resistant organisms between hospitals. The model framework allows for heterogeneity in hospital size and highlights the importance of large hospitals in the maintenance of resistant organisms within a defined country. The spread of methicillin resistant *Staphylococcus aureus* (MRSA) in England and Wales provides a template for model construction and analysis. The final section addresses the emergence and spread of resistant organisms in communities of people and the dependence on the intensity of selection as measured by the volume or rate of drug use. Model output is fitted to data for Finland and Iceland and conclusions drawn concerning the key factors determining the rate of spread and decay once drug pressure is relaxed.

Keywords: antibiotic resistance; transmission dynamics; epidemiology; pharmacodynamics; nosocomial infection; mathematical models

1. INTRODUCTION

Genetic diversity is a characteristic of microbes, whether their lifestyle is free-living or parasitic. The last few years has seen rapid advances in our understanding of the genetic diversity within bacterial populations and the structures of the genetic codes of a series of important species, including some major pathogens of humans such as *Mycobacterium tuberculosis* (Cole *et al*. 1998). One aspect of this genetic diversity and the potential for rapid evolution within bacteria that is of major public health significance worldwide is the emergence and spread of antibiotic resistance in a wide variety of organisms that infect humans, and birds plus mammal species within the agricultural industry. Today many view the evolution and spread of antibiotic resistance as the major public health crisis of the late part of this century, with the evolution of bacteria within hospital settings that are resistant to all major antibiotics a distinct possibility in the very near future.

The study of antibiotic resistance is a field that has largely been the preserve of the microbiologist and the infectious disease clinician responsible for the care of patients with bacterial infections. Until recently, most have had confidence in the pharmaceutical industry to keep one step ahead of the microbe in terms of producing new antibiotics that can combat infection by organisms resistant to the previous generations of drugs. To date that has certainly been the case. However, the rate of discovery of new compounds has slowed considerably over the past three decades, in part due to the very high costs of research, development and testing prior to the successful launch of a new antibiotic. In discussions of how best to combat resistance or how to slow its spread, the debates have largely centred on the microbiological and clinical issues. Very few papers in this important field address the key population genetic issues that underpin an understanding of the evolution and spread of resistant organisms (Björkmann *et al*. 1998; Stilianakis *et al*. 1998; Blower *et al*. 1998; Levin *et al*. 1997; Austin *et al*. 1997*a*,*b*; Bonhoeffer *et al*. 1997; Schrag *et al*. 1997; Lenski 1997; Lenski *et al*. 1994; Massad *et al*. 1993). An even smaller number attempt to meld current understanding of the transmission dynamics of bacteria in human communities

(including hospitals), with the key population genetic factors (Levin *et al*. 1997; Austin *et al*. 1999; Bonhoeffer *et al*. 1997). The number of publications that meld these two areas, in combination with an understanding of the mechanisms of the evolution of resistance, patterns of drug consumption and the pharmacokinetics and pharmacodynamics of defined drugs and pathogens, can be counted on one hand (Lipsitch & Levin 1997; Austin *et al*. 1998*b*).

The general issue is that an interdisciplinary approach is needed to interpret correctly current patterns of evolution and spread, plus address the issue of how best to manage antibiotic resistance in both the healthcare and community settings. Techniques and concepts from a wide variety of different fields must be harnessed, such as those in pharmacology, microbiology, population genetics and epidemiology. A powerful template to merge the methods and concepts of these different fields of scientific study can be constructed by the sensible use of simple and complex mathematical models of the key biological processes. The case for the use of a mathematical framework is made even more compelling by the strong existing traditions for the use of mathematical methods in the fields of pharmacology, population genetics and epidemiology.

In this paper we present some recent research that melds different components of these various fields to address problems at a series of different levels of study. These include the evolution of resistance within the treated host, the spread of resistance within and between hospital settings, and the epidemiology and evolution of resistance in communities of people. Our approach is the use of simple mathematical templates and our aim is to shed light on the key factors that control observed patterns of antibiotic resistance and how drug use can be tailored to slow the likelihood of evolution and rapid spread. A central problem in management is the key principle that the stronger the selective pressure, the more rapid will be the pace of evolution to meet this pressure. The frequency of antibiotic resistant organisms in a defined population of bacteria is invariably related to past or current patterns of drug use. To alter frequency it is necessary to change the direction of selection. How best to do this will depend on the precise details of host, bacteria and drug. However, a precise mathematical template for study helps identify what needs to be measured and the key processes determining observed pattern.

2. WITHIN-HOST MODELS OF INFECTION AND ANTIBIOTIC TREATMENT

The use of mathematical models for the analysis of viral infections such as HIV has resulted in considerable advances in our understanding of both disease progression and the impact of drug therapy (Ho *et al*. 1995; Wei *et al*. 1995; Bonhoeffer *et al*. 1996; Austin *et al*. 1998*b*). In the case of bacterial infections, where within-host dynamics is not so easily measurable, there have been fewer advances (Lipsitch & Levin 1997). In the pharmacological research literature, mathematical models of drug absorption and elimination kinetics have been widely used. This field of study is referred to as pharmacokinetics (Rowland & Tozer 1995; Austin *et al*. 1998*b*). A large amount of data are available on the pharmacokinetics of antibiotic agents which can be usefully employed in mathematical models of bacterial infection and treatment. The effect of an antibiotic on the target pathogen usually correlates with the concentration of the drug in the habitat of the pathogens. The study of dynamical response of the infectious agent in the presence of the drug is termed pharmacodynamics (Löwdin *et al*. 1998; Aeschlimann *et al*. 1998; Berg *et al*. 1996; Hyatt *et al*. 1995; Drusano *et al*. 1993) and provides the link between pharmacokinetics and models of within host pathogen population dynamics (Austin *et al*. 1998*b*).

(a) *Pharmacokinetics and pharmacodynamics*

Antibiotics may be administered either orally, intramuscularly or intravenously, and the eventual concentration of active drug at the site of infection will be determined by the dose, the route of administration and the dosage regimen. Dosage regimens are designed to maintain drug concentrations at therapeutic levels, and must balance issues of both toxicity and efficacy (Rowland & Tozer 1995). For simplicity, we concentrate on changes in the concentration, $C(t)$, of a single antibiotic given at a dose, D, to a host with volume of distribution V such that $C_0 = D/V$, where C_0 is the initial concentration. If absorption is rapid (i.e. can be ignored) or the antibiotic is given intravenously, and elimination follows first-order kinetics (as is common during the early stages of elimination), then the plasma concentration at time t is determined by

$$\frac{\mathrm{d}C}{\mathrm{d}t} = -kC, \tag{1}$$

$$C(t) = C_0 \exp(-kt), \tag{2}$$

where k is the elimination constant and the half-life of the drug is $t_{1/2} = \ln(2)/k$. Assuming doses are given at discrete times $t = 0$, $t = \tau$, $t = 2\tau$, etc. then the concentration immediately after i doses will be

$$C_i = C_0 \frac{1 - r^i}{1 - r}, \tag{3}$$

where $r = \exp(-k\tau)$ is the decay factor. After several doses the regimen reaches equilibrium and the concentration $C(t)$ lies between the limits $rC_{\max} \leqslant C(t) \leqslant C_{\max}$ where $C_{\max} = C_0\mathcal{R}$ and $\mathcal{R} = 1/(1 - r)$ is called the accumulation factor. Typically, the impact of a drug in a defined pathogen population saturates with increasing drug concentration. Suggested reasons for this saturation include metabolic effects such as enzyme production and a fixed number of sites where a drug can act on the invading organism. We use the so-called $E_{\max}$ saturating model, where if E is the effect of the drug (e.g. per capita death rate of the bacteria due to the action of the drug at concentration C), then

$$E(C) = \frac{E_{\max}C^n}{C_{50}^n + C^n}. \tag{4}$$

Hence, $E_{\max}$ denotes the maximum effect, C_{50} the concentration at half effect and n is a shape factor denoting the slope of the curve.

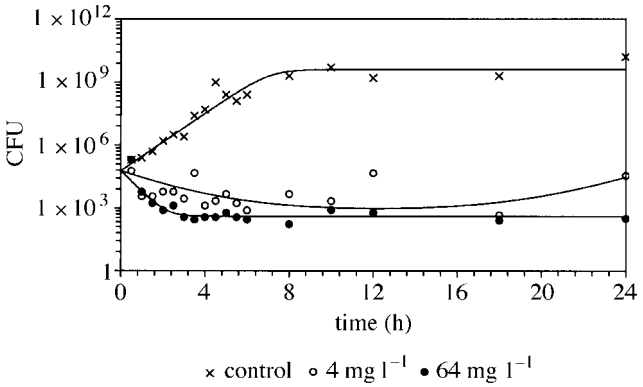

Figure 1. *In vitro* pharmacodynamic effect of imipenem killing of *Pseudomonas aeruginosa* at concentrations of 0, 4 and 64 mg l^{-1}. Data are shown from Berg *et al.* (1996). Parameters used are $\lambda = 1.6\ h^{-1}$, $N(0) = 10^5$, $K = 3.2 \times 10^9$ CFU (colony forming unit), $\alpha = 4\ h^{-1}$, $C_{50} = 3$ mg l^{-1}, $n = 1.2$. Imipenem is eliminated from the system with constant $k = 0.054\ h^{-1}$.

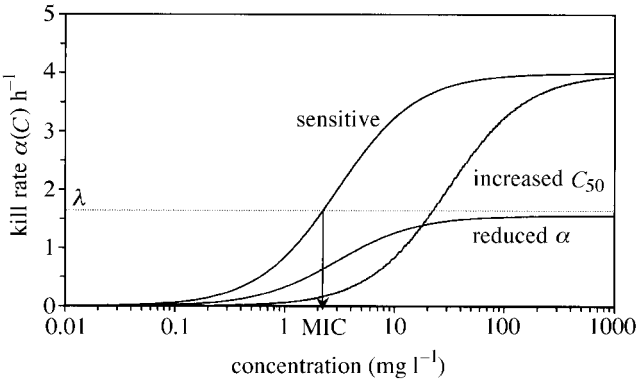

Figure 2. Concentration–kill rate curve for imipenem killing of *Pseudomonas aeruginosa*, with MIC for sensitive (MIC = 2 mg l^{-1}) and resistant strains showing the effects of (i) increased C_{50} (MIC =10 times sensitive value), and (ii) reduced saturating kill rate, α. Pharamacodynamic parameters are as figure 1. Increased C_{50} resistance implies that increasing the dose can always give therapeutic concentrations (toxicity issues aside).

Many of the pharmacodynamic studies of antibiotic effect involve growth curves, in which an organism is grown in varying concentrations of drug either *in vitro* or *in vivo* (Löwdin *et al.* 1998; Aeschlimann *et al.* 1998; Berg *et al.* 1996; Hyatt *et al.* 1995). In order to model these growth curves we require a mathematical model of the population growth of bacteria. If $\lambda(N)$ is the net growth rate of a bacteria if N organisms are present (allowing for density dependence) and $\alpha(C)$ the bacterial kill rate at drug concentration C, then in the absence of any post antibiotic effect,

$$\frac{dN}{dt} = \lambda(N) - \alpha(C)N. \tag{5}$$

For *in vitro* studies $\lambda(N) = \lambda N(1 - N/K)$ where K is a carrying capacity determined by the experiment. This simple model can be used to fit experimental data providing a concentration–kill rate pharmacodynamic curve (figure 1). In this dynamical model a minimum inhibitory concentration (MIC) can be defined as the concentration which just inhibits bacterial growth i.e. $\alpha(C) = \lambda$, or equivalently,

$$\mathrm{MIC} = (1 - \epsilon)^{-1/n} C_{50} \tag{6}$$

where $\epsilon = \lambda/\alpha$ is the ratio of maximum kill rate to net growth rate. For bacteriostatic antibiotics (e.g. macrolides) the net growth rate becomes a function of drug concentration, $\lambda(C)$, however the conclusions from our analyses will remain unchanged.

The effects of antibiotic resistance will manifest themselves via the pharmacodynamics of antibiotic action. Conventional measures of antibiotic resistance take the form of MIC determination and categorization via breakpoints. An increased MIC may be a result of any combination of three factors determined by the form of equation (6). First, C_{50} may increase, thereby shifting the overall curve to the right in a linear manner. Second, ϵ may decrease thereby reducing the peak bactericidal kill rate, α. Third, the shape function, n may increase (although this effect will be minimal). Since pharmacodynamic studies have thus far tended to focus on sensitive organisms, the precise pharmacodynamic effects of antibiotic resistance remain uncertain (figure 2). It is, however, important that these effects be quantified, as they have profound influences on the usefulness of a drug. For example, if C_{50} increases then the saturating bactericidal kill rate α can still be reached (for a sufficiently high dose, D), hence clinical improvement may be seen by doubling the dose of amoxicillin for infections with reduced sensitivity (as proposed in Spain). If, however, bactericidal activity is reduced, then no increase in dose will ever be able to compensate for the loss of sensitivity and the clinical lifetime of the drug cannot be increased. Typical mechanisms for antibiotic resistance may include efflux whereby the drug is pumped out of the cell (e.g. *Pseudomonas aeruginosa* resistance to imipenem (Livermore 1992)), altered target site (e.g. penicillin-binding protein) and deactivation of the drug by enzymes (e.g. beta-lactamase resistance) (see Salyers & Whitt (1994) for further details). For drug efflux the first pharmacodynamic effect would appear most likely, the drug is at a reduced concentration within the cell. Where the target site is altered, increasing concentration will obviously have little effect. When a drug is broken down by enzyme activity, increasing the number of sites can restore sensitivity, as has been demonstrated by the use of clavulanic acid added to amoxicillin (Nahwani & Wood 1993).

(b) *Mathematical models of antibiotic therapy*

Pharmacodynamic models provides the ideal template for constructing models of antibiotic therapy and the emergence of resistance. Once the concentration–kill rate curve is known, equation (5) can be solved under given assumptions, such as exponential growth of the bacteria in the absence of a drug, multiple dosing, multiple strains and the influence of acquired immunity. We use the complete E_{max} model throughout and begin by considering the effects of multiple dosing during exponential growth (Lipsitch & Levin 1997). Dividing equation (5) by N, gives the simplified form

$$\frac{d \ln N}{dt} = \lambda - \frac{\alpha C_0^n \exp(-kn(t - t_0))}{C_{50}^n + C_0^n \exp(-kn(t - t_0))}, \tag{7}$$

which has the general solution

$$N(t)=N(t_0)\exp(\lambda\tau)\left(\frac{C_{50}^n+C_0^n\exp(-kn(t-t_0))}{C_{50}^n+C_0^n}\right)^{\alpha/kn}. \quad (8)$$

If treatment occurs at discrete times (as in the multiple dosing regimen), then the change in $\ln N$, $\Delta\ln N_i=\ln N_{i+1}-\ln N_i$, after dose i (i.e. $t=(i+1)\tau$) is given by

$$\Delta\ln N_i=\lambda\tau+\frac{\alpha}{kn}\ln\left(\frac{C_{50}^n(1-r)^n+C_0^n r^n(1-r)^{ni}}{C_{50}^n(1-r)^n+C_0^n(1-r)^{ni}}\right). \quad (9)$$

Therapeutic regimens require that $\Delta\ln N_i\leqslant 0$ (as an absolute minimum), which gives a threshold concentration $C_0\geqslant C_{\min}$ for a given decay parameter, $r=\exp(-k\tau)$,

$$C_{\min}(i)=\mathrm{MIC}\left(\frac{1-r}{1-r^{i+1}}\right)\left(\frac{(1-\epsilon)(1-r^{n\epsilon})}{r^{n\epsilon}-r^n}\right)^{1/n}, \quad (10)$$

depending on dose i. For the first dose

$$C_{\min}(0)=\mathrm{MIC}\left(\frac{(1-\epsilon)(1-r^{n\epsilon})}{r^{n\epsilon}-r^n}\right)^{1/n}, \quad (11)$$

and at equilibrium ($i\to\infty$) $C_{\min}(\infty)=C_{\min}(0)/\mathcal{R}$. For example, suppose an antibiotic is given every half-life ($\mathcal{R}=2$) and $\epsilon=0.5$ (i.e. $\mathrm{MIC}=C_{50}$) and $n=1$. For the first dose $C_{\min}(0)=\mathrm{MIC}\sqrt{2}$ for therapeutic benefit, whereas once equilibrium is reached $C_{\min}(\infty)=\mathrm{MIC}/\sqrt{2}$. Figure 3 shows the effect of multiple dosing on the pharmacodynamics of imipenem acting against *Pseudomonas aeruginosa* ($\mathrm{MIC}=1\,\mathrm{mg\,l^{-1}}$ and $10\,\mathrm{mg\,l^{-1}}$). Elimination of the antibiotic reduces the kill rate from a peak (determined by both the dose and the MIC), and dosing returns the kill rate back up the curve. Since the concentration is plotted on a log scale and elimination is assumed to be first order (i.e. exponential), the length of the curve is proportional to time. Therapeutic regimens must keep the kill rate, $\alpha(C)$, above the net growth rate, λ, of the bacterium, which is shown for the sensitive strain ($\mathrm{MIC}=1\,\mathrm{mg\,l^{-1}}$). The resistant strain ($\mathrm{MIC}=10\,\mathrm{mg\,l^{-1}}$) will however show net growth because the dose (and hence $C_0=D/V$) is below the minimum required for therapeutic activity, $C_{\min}$.

(i) *Dose splitting: the effect of multiple dosing*

Dosage regimens are typically expressed in the form $C_\tau q\tau$, i.e. a concentration C_τ given every time period τ. 500 mg of penicillin given every 6 h ($500q6$) could equally be administered as 250 mg every 3 h ($250q3$). We write this as $aC_\tau qa\tau$ where $a\leqslant 1$. If a regimen is subdivided into $1/a$ subdoses at intervals $\tau'=\tau/a$ then the total log reduction in bacteria, $\Delta\ln N(a)$ is given by

$$\Delta\ln N(a)=\Delta\ln N(a)|_{0\to\tau'}+\Delta\ln N(a)|_{\tau'\to 2\tau'}+\ldots+\Delta\ln N(a)|_{(1-a)\tau'/a\to\tau'/a}. \quad (12)$$

Summing individual terms using equation (9) gives a total log reduction

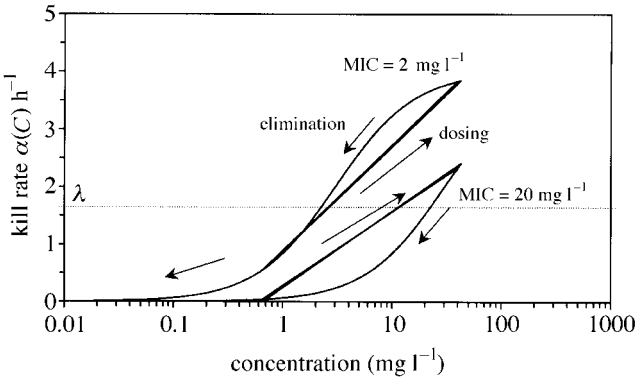

Figure 3. Effect of dosing on kill rate for sensitive ($\mathrm{MIC}=2\,\mathrm{mg\,l^{-1}}$) and resistant ($\mathrm{MIC}=20\,\mathrm{mg\,l^{-1}}$) strains. First-order elimination means that time is proportional to length of curve.

$$\Delta\ln N(a)=\lambda\tau+\frac{\alpha}{kn}\ln\prod_{i=1}^{1/a}\frac{C_{50}^n(1-r^a)^n+(r^aaC_0)^n(1-r^{ia})^n}{C_{50}^n(1-r^a)^n+(aC_0)^n(1-r^{ia})^n}. \quad (13)$$

For fixed total drug, C_0, and constant pharmacodynamics, in the limit as τ becomes large and r becomes small,

$$N(\tau,a)\simeq N_0\exp(\lambda\tau)\left(\frac{1}{1+(aC_0/C_{50})^n}\right)^{\alpha/kna}. \quad (14)$$

In other words, bacterial abundance in the patient is reduced as a increases. The implications for antibiotic therapy are that splitting a dose can maximize therapeutic effect, depending on pharmacodynamic parameters. This has been demonstrated numerically (Lipsitch & Levin 1997), but equation (14) provides a clearer understanding of the phenomenon.

(ii) *The influence of acquired immunity*

The assumption of exponential population growth is only valid if density-dependent effects such as competition for resources and effect or immune responses are not acting within the host. Acquired immunity means that most community-acquired infections are self-limiting, although morbidity may be considerable depending on the degree to which immunological responses can control pathogen growth. For example, in the absence of resistant strains, if $I(t)$ is the measure of the severity of immunological responses directed at the pathogen (i.e. specific T or B cells) at time t and $1/\mu$ is the average duration of the immune response (i.e. effector cell life expectancy), then

$$\frac{\mathrm{d}N}{\mathrm{d}t}=\lambda(N)N-\gamma IN, \quad (15)$$

$$\frac{\mathrm{d}I}{\mathrm{d}t}=\Lambda(N)-\mu I, \quad (16)$$

where γ is the per capita cell mediated immune effect (bactericidal activity) and $\Lambda(N)$ the immune proliferation function in response to the abundance of the invading bacteria. If $\Lambda(N)=\Lambda_0$ (e.g. macrophage invasion of a site of infection), and $\lambda(N)=\lambda$ (exponential

growth) then the exact solution of these equations is possible:

$$N(t)=N(0)\exp(\lambda t)\exp(-xt+x(1-\exp(-\mu t))/\mu), \quad (17)$$

$$I(t) = I_0(1-\exp(-\mu t)), \quad (18)$$

where $I_0 = \Lambda_0/\mu$ is the maximum immune response and $x = \gamma I_0/\lambda$ is the ratio of immune killing to net bacterial growth rate. If $x>1$ then the immune response can control the infection and the bacteria reach a maximum population at a time

$$t_{\max} = \frac{1}{\mu}\ln\frac{x}{x-1}, \quad (19)$$

depending on the persistence of the immune response, $1/\mu$. If bacterial growth is logistic, i.e. $\lambda(N) = \lambda(1-K/N)$ clearance is also possible provided $x>1$. Where the immune response proliferates in response to the total bacterial population we assume a saturating response of the form

$$\Lambda(N) = \Lambda_0 + \frac{aIN}{b+\phi N}, \quad (20)$$

where a is the maximum per capita proliferation rate, b is the bacterial population which gives half the maximum rate and ϕ determines the form of proliferation ($\phi = 0,1$ with saturation when $\phi = 1$). Where resistant strains are also present $N = N_s + N_r$. If some fitness cost is associated with resistance (e.g. reduced growth rate, $\lambda' \leqslant \lambda$), the full model takes the form

$$\frac{dN_s}{dt} = \lambda N_s - \alpha(C,\mathrm{MIC}_s)N_s - \gamma I N_s, \quad (21)$$

$$\frac{dN_r}{dt} = \lambda' N_r - \alpha(C,\mathrm{MIC}_r)N_r - \gamma I N_r, \quad (22)$$

$$\frac{dI}{dt} = \Lambda(N) - \mu I. \quad (23)$$

Numerical evaluation of these equations (figure 4) shows that for self-limiting infections the overall immune response, $I(t)$, will be determined by both the degree of resistance (measured by MIC_r) and the time elapsed before treatment begins. For example, early treatment will reduce the total bacterial population, N (i.e. morbidity), and, in doing so, the resulting immune response (thereby increasing susceptibility to subsequent infections). The reduction in immunity, which is what clears highly resistant strains, will also produce a proportionately more resistant infection (albeit with reduced morbidity), which may have transmission consequences for other hosts. These consequences will be discussed in greater detail in § 5.

3. TRANSMISSION DYNAMICS OF ANTIBIOTIC RESISTANT PATHOGENS IN HOSPITALS

The continued evolution of antibiotic resistance in common hospital pathogens presents an ever-increasing threat to public health. Organisms once considered of low invasive potential now give cause for concern in immuno-

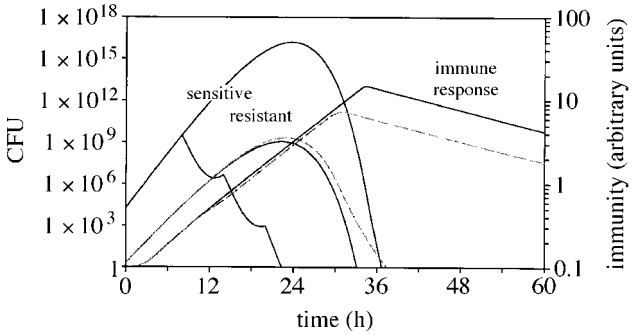

Figure 4. Within-host dynamic model of self-limiting bacterial infection showing the effects of antibiotic treatment (dashed lines) on bacterial population size and acquired immunity. Antibiotic treatment produces lower morbidity with lower immunity. Parameters used are as in figure 1 with $\lambda' = 1.2\,\mathrm{h}^{-1}$, $\gamma = 0.5\,\mathrm{h}^{-1}$, $a = 0.2\,\mathrm{h}^{-1}$, $b = 10^6$, $\phi = 1$, $\mu = 0.05\,\mathrm{h}^{-1}$, $I_0 = 0.1$, $N_s(0) = 2\times10^4$, $N_r(0) = 2$ and $I(0) = I_0$.

compromised hosts. The recent emergence of vancomycin-resistant enterococci (VRE) as a nosocomial pathogen is a striking example of this new danger to vulnerable patients. Treatment options are often limited to combining antimicrobials or experimental compounds of unproven efficacy. Other pathogens, such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), have also developed multiple resistance and give even greater cause for concern. Reports of MRSA strains with reduced susceptibility to vancomycin (Hiramatsu *et al.* 1997; Tabaqchali 1997), suggest that unless there is a return to conventional practices of infection control, with its emphasis on reduced transmission, antibiotic therapy may not be possible in the near future for some hospital acquired infections.

Many factors contribute to make hospitals a favourable environment for the development of resistance, not least of which is the broad spectrum of antimicrobials used to treat infection (Tenover & McGowan 1996). Another important factor is the frequent mixing of patients and health-care workers (HCWs)—for whom asymptomatic carriage is a potential threat. Although some emphasis has been placed on the population dynamics of competition between resistant and susceptible bacteria (Massad *et al.* 1993; Bonhoeffer *et al.* 1997), little work has been completed to date with regards to the transmission dynamics of resistant infections within frameworks that meld genetics and epidemiology (Austin *et al.* 1998*a*; Sebille *et al.* 1997). Many hospital pathogens are capable of colonizing patients without inducing overt symptomatic infection. This generated the belief that new hospital outbreaks were a consequence of endogenous activation from patient sources or environmental contamination. However studies of both VRE and fungal pathogens have demonstrated that indirect transmission via the hands of transiently contaminated HCWs is a very important determinant of colonization and infection (Sanchez *et al.* 1992; Bonten *et al.* 1996).

(a) *Indirect transmission models of colonization*

Patients are classified as either uncolonized (X_p) or colonized (Y_p). Given the rapid turnover in patients and long duration of colonization, once colonized, patients are assumed to remain so for the duration of their stay in the

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

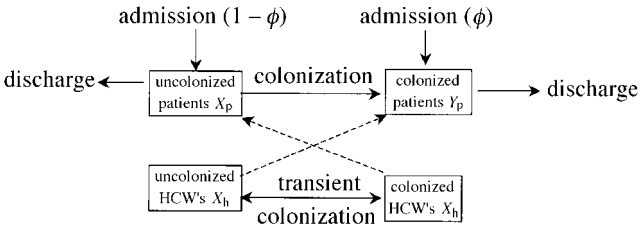

Figure 5. Mathematical framework for indirect patient–HCW–patient transmission of colonizing bacteria within an ICU. Prevalence of colonization on admission is denoted by ϕ (see text for equations).

ward or intensive-care unit (ICU). The number of HCWs is assumed to be fixed (N_h), and HCWs are also assumed to be either uncolonized (X_h) or transiently colonized (Y_h). The transmission dynamics can be described by four ordinary differential equations (figure 5):

$$\frac{dX_p}{dt} = (1-\phi)\Lambda - \mu X_p - cb_p Y_h X_p, \tag{24}$$

$$\frac{dY_p}{dt} = \phi\Lambda - \mu Y_p + cb_p Y_h X_p, \tag{25}$$

$$\frac{dX_h}{dt} = -cb_h Y_p X_h + \gamma Y_h, \tag{26}$$

$$\frac{dY_h}{dt} = -\frac{dX_h}{dt}, \qquad X_h + Y_h = N_h, \tag{27}$$

where Λ is the patient admission rate, ϕ the prevalence of colonization at admission, $D_p = 1/\mu$ the average patient's length of stay (LOS) (typically days), c is the HCW–patient contact rate, b_h and b_p the respective probabilities of transmission from patient→HCW and HCW→patient, and $D_h = 1/\gamma$ the average duration of transient colonization (typically hours).

Optimal use of available resources frequently requires that available beds be always occupied (i.e. $X_p + Y_p = N_p = \Lambda/\mu$). Under this assumption the respective colonization prevalences for patients ($y_p(t) = Y_p(t)/N_p$) and HCWs ($y_h(t) = Y_h(t)/N_h$) are determined by the two differential equations:

$$\frac{dy_p(t)}{dt} = \mu(\phi + R_p y_h(1-y_p) - y_p), \tag{28}$$

$$\frac{dy_h(t)}{dt} = \mu'(R_h y_p(1-y_h) - y_h), \tag{29}$$

where $R_h = b_h c N_p D_h$ and $R_p = m b_p c N_p D_p$ are the respective HCW–patient and patient–HCW reproductive numbers, and $m = N_p/N_h$ is the staff–patient ratio (typically 1:1 for ICUs and less for general wards). Because transmission is via patient–HCW–patient, the overall reproductive number for transmission, R_0, takes the composite form

$$R_0 = m b_p b_h (cN_p)^2 D_p D_h. \tag{30}$$

The endemic prevalences are given by

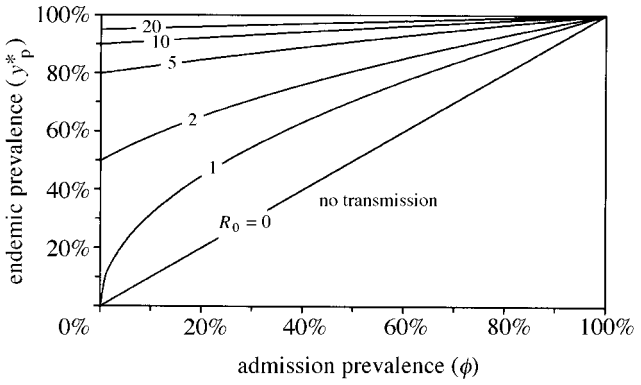

Figure 6. Endemic colonization prevalence for patients, y_p^*, as a function of admission prevalence, ϕ. Admission of colonized patients can stabilize transmission when the reproductive number falls below unity. Where $y_p^* > \phi$, indirect transmission can be implicated.

$$y_p^*(\phi) = \frac{R_0 - 1 + \phi R_h + \sqrt{(R_0 - 1 + \phi R_h)^2 + 4\phi(R_0 + R_h)}}{2(R_0 + R_h)}, \tag{31}$$

$$y_h^*(\phi) = \frac{R_h p^*(\phi)}{R_h p^*(\phi) + 1} \tag{32}$$

(figure 6). If new admissions are carefully screened and colonized patients isolated from the ward (i.e. $\phi = 0$), the closed system reduces to the Ross–Macdonald model for malaria transmission (Anderson & May 1991), with vector–host ratio m and biting rate $a = cN_p$. The endemic solution takes the simple symmetrical form

$$y_p^*(0) = \frac{R_0 - 1}{R_0 + R_h}, \qquad y_h^*(0) = \frac{R_0 - 1}{R_0 + R_p}. \tag{33}$$

Where there is a considerable separation in time-scales (as in this instance), there will be a large difference in endemic prevalences. Typically $R_p \gg 1$ and $R_h \ll 1$, only the product $R_0 = R_p R_h$ must be greater than unity for transmission. Therefore in endemic settings the model predicts that $y_p^* \gg y_h^*$, providing one explanation of the observational finding that culturing the hands of HCWs seldom provides pathogen isolates (Morris *et al.* 1995).

(i) *Hand-washing*

Hand-washing by HCWs between patient contacts reduces the probability b_p that they will transmit the pathogen to their next patient. If p is the efficacy of hand-washing protocols (equal to the compliance rate times the efficacy/wash), then $R_0(p) = (1-p)R_0$. Transmission can be curtailed (and colonization eradicated) provided $R_0(p) < 1$, i.e. if p exceeds the threshold rate $p_c = 1 - 1/R_0$ and new admissions are screened ($\phi = 0$). Even if washing hands is 100% effective, the threshold compliance rate can be very high for modest values of R_0. Studies show reported compliance rates of 20–40% (Albert & Condie 1981; Simmons *et al.* 1990; Doebbelling *et al.* 1992). If R_0 is in excess of 1.25–1.67, hand-washing measures alone are unlikely to be sufficient for controlling endemic transmission.

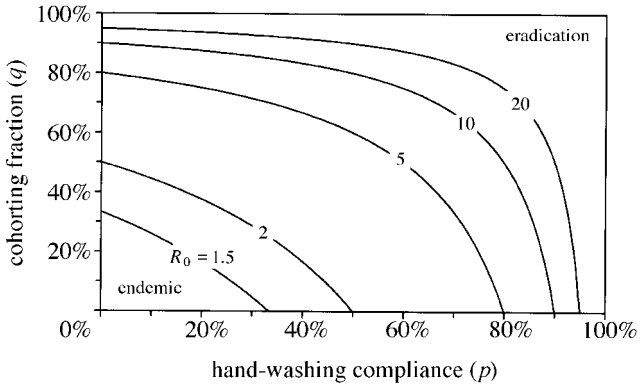

Figure 7. Threshold eradication criteria needed to eradicate endemic colonization when $\phi = 0$ and infection control practices are combined. Observed hand-washing compliances of 20–40% are unlikely to eradicate endemic colonization alone.

(ii) *Management of HCWs*

Introducing more HCWs into a ward can either reduce or increase transmission levels, depending upon the management of the ward. Where HCW resources are limited, increasing the number of HCWs will increase transmission due to an increased number of contacts between HCWs and patients. Conversely in the ICU, where resources are less limited, increasing the numbers of HCWs reduces transmission because individual staff workloads are reduced. Cohorting HCWs on a 1:1 basis can provide a very effective method of limiting transmission. If q is the conditional probability that a HCW returns to the same patient rather than visiting another patient, then the effective HCW–patient ratio $m(q) = m(1-q)$. Using the same argument as above, there is a threshold cohorting rate $q_c = 1 - 1/R_0$. Effective measurement of cohorting rates have yet to be reported. However given that 1:1 HCW–patient ratios are not unusual in ICU settings, cohorting rates are likely to exceed those of hand-washing providing a possible focus for resource allocation (figure 7).

(b) *Stochastic considerations*

Since the number of HCWs and patients is typically small (less than 30) in most hospital settings, stochastic fluctuations will play an important role in determining the course of an outbreak. When modelling any single outbreak a full stochastic realization of equations (24)–(27) is required (Renshaw 1991; Anderson & May 1991) (figure 8*a*). Where there is a significant separation of time-scales and the number of patients remains constant, the quasi-steady state (QSS) approximation ($\mathrm{d}\Upsilon_\mathrm{h}/\mathrm{d}t \simeq 0$) can be used to reduce equations (24)–(27) to

$$\frac{\mathrm{d}y_\mathrm{p}}{\mathrm{d}t} = \phi\mu + \frac{\mu R_0 y_\mathrm{p}(1-y_\mathrm{p})}{1+R_\mathrm{h}y_\mathrm{p}} - \mu y_\mathrm{p}. \qquad (34)$$

An explicit closed solution of this equation is only possible in the limit $R_\mathrm{h}y_\mathrm{p} \to 0$, which is the logistic equation with immigration of new infectives (Appendix A). In the absence of colonized admissions ($\phi = 0$) the quasi-equilibrium probability distribution π_i, that i patients will be endemically colonized, can be calculated (figure 8*b*). Smaller wards and ICUs with few beds will have large fluctuations in prevalence. For example, if $R_0 = 2$ and

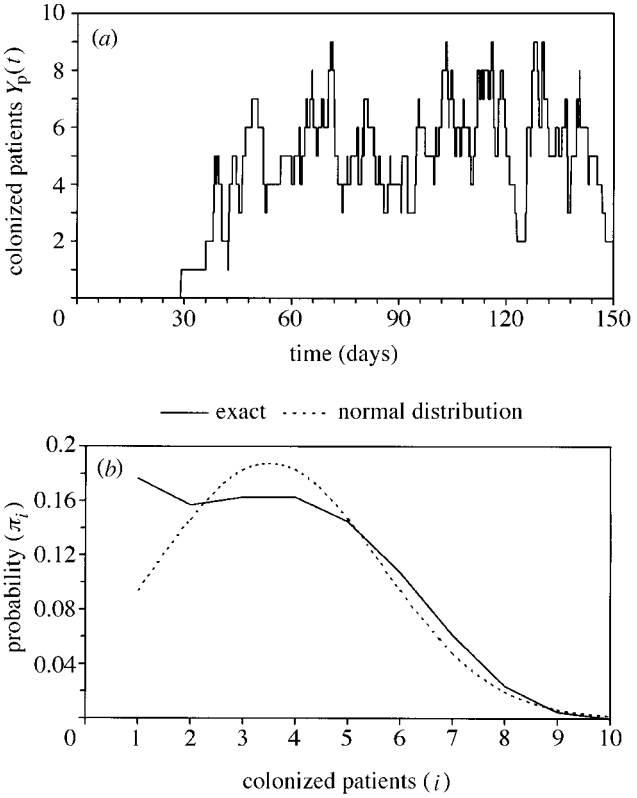

Figure 8. (*a*) Stochastic realization of the indirect transmission model showing an outbreak stabilized by colonized admissions. Parameters used are $R_0 = 2$, $N_\mathrm{p} = 9$, $N_\mathrm{h} = 9$, $c = 4.2$ patient^{-1} HCW^{-1} day^{-1}, $D_\mathrm{p} = 7$ days, $D_\mathrm{h} = 1$ h, $b_\mathrm{p} = b_\mathrm{h} = 10\%$, $\Lambda = 2\,\mathrm{day}^{-1}$ and $\phi = 0.05$. Mean occupancy is 84.8% and with mean endemic prevalence 49.8%. (*b*) Quasi-equilibrium probability distribution, π_i, that i patients will be endemically colonized assuming $\phi = 0$.

$N_\mathrm{p} = 9$ beds, the predicted 95% confidence region for y_p^* is $y_\mathrm{p}^* \simeq 38.9 \pm 46.2\%$. The magnitude of fluctuations when patient numbers are small implies that identifying trends in endemic settings, perhaps induced by changes in management practices, will be very difficult.

(c) *The emergence of resistance*

The previous theoretical framework of indirect transmission is equally applicable to both antibiotic-sensitive and -resistant pathogens. However, it does not take into account any measure of the selection pressure exherted by antibiotic treatment. When more than one bacterial strain is present the framework must be modified accordingly to reflect all available therapy combinations. For analytical simplicity we retain the QSS approximation and take the limit $R_\mathrm{h} \to 0$ in the closed model of equation (34).

Within an ICU, the majority of patients will receive an antibiotic, either as prophylaxis (e.g. digestive decontamination) or for the treatment of overt infection (e.g. vancomycin for staphylococcal wound infections). Antibiotic therapy may select for resistance by either of two mechanisms. First, treatment may induce or select pre-existing resistant organisms within a host (so-called acquired resistance). Second, by killing off the existing host flora, antibiotic treatment increases the susceptibility to colonization by resistant bacteria. Patients who become colonized with resistant flora may then develop overt

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

infection and subsequently have an increased LOS, which in turn increases opportunities for further transmission. Earlier work on antibiotic management has focused on the effects of treatment on reducing durations of infection, as might be expected for upper respiratorytract infection (Massad *et al*. 1993; Bonhoeffer *et al*. 1997). We use a similar framework to focus on the effects in ICU settings.

(i) *Single drug therapy*

We begin by considering the case when only a single antibiotic (or class of antibiotics if resistance patterns are common) is in use. Using the QSS approximation and assuming that all admitted patients are uncolonized ($\phi = 0$), the prevalence of colonization for sensitive (y_p) and resistant (y'_p) strains are determined by the equations

$$\frac{dy_p}{dt} = \mu y_p(R_0(1 - y_p - y'_p) - 1) - \mu a\sigma y_p, \tag{35}$$

$$\frac{dy'_p}{dt} = \mu' y'_p(R'_0(1 - y_p - y'_p) - 1) + \mu a\sigma y_p, \tag{36}$$

where a is the proportion of patient stay for which antibiotics are administered, σ the probability of acquired resistance during treatment and primes denote parameters for the resistant strain. Switching parameters, let y denote the prevalence of colonization ($y = y_p + y'_p$) and f the frequency of resistance ($f = y'_p/y$), then

$$\frac{dy}{dt} = y[(\mu R_0(1 - f) + \mu' R'_0 f)(1 - y) - \mu(1 - f) - \mu' f], \tag{37}$$

$$\frac{df}{dt} = f(1 - f)[(\mu' R'_0 - \mu R_0)(1 - y) + \Delta\mu] + (1 - f)\mu a\sigma, \tag{38}$$

where $\Delta\mu = \mu - \mu' \geqslant 0$. If transmission is unaffected by antibiotic treatment (e.g. infection control practices limit the spread of both strains), df/dt can be solved exactly. If f_0 is the frequency of resistance at time t_0, f is determined by the logistic solution,

$$f(t) = \frac{(f_0 + \epsilon)\exp(\Delta\mu(1 + \epsilon)(t - t_0) - \epsilon(1 - f_0)}{(1 - f_0) + (f_0 + \epsilon)\exp(\Delta\mu(1 + \epsilon)(t - t_0)}. \tag{39}$$

The parameter ϵ measures the selective pressure of acquired resistance (since there is no difference in transmission) and is determined by $\epsilon = a\sigma(1 + 1/q)$, where q is the percentage increase in LOS for resistantly colonized patients ($q = (D'_p - D_p)/D_p$). In the limit $\sigma = 0$ (no acquired resistance), if $f_0 > 0$ then $f \to 1$ and resistance will tend to fixation at a rate independent of antibiotic treatment. This is simply a consequence of resistantly colonized patients remaining in the ICU longer and therefore having a higher reproductive number ($R'_0 > R_0$). The characteristic time-scale for the ecological replacement of sensitive colonization is of order $1/\Delta\mu$, irrespective of antibiotic consumption. Where antibiotic treatment induces acquired resistance and no resistance is present at time t_0, the time for resistance to reach 50% of cases, T_{50} is given by

$$T_{50} = \frac{\ln(2 + 1/\epsilon)}{\Delta\mu(1 + \epsilon)}. \tag{40}$$

Typically if $D = 7$ days, $q = 25\%$ ($D' = 1.25D$), $a = 80\%$ of patient stay and $\sigma = 10\%$, then $\epsilon = 0.04$ and $\Delta\mu = 0.0286$ week^{-1}, giving $T_{50} = 48$ days. Halving antibiotic consumption increases T_{50} to 59 days, demonstrating that ecological replacement of sensitive colonization is playing a dominant role.

The selective transmission advantage antibiotic-resistant strains have is likely to play a considerable role in the overall emergence of resistance. If LOS is unaffected by antibiotic treatment (i.e. $\Delta\mu \simeq 0$) and acquired resistance minimal ($\sigma = 0$), then

$$\frac{df}{dt} = \mu f(1 - f)(R'_0 - R_0(a))(1 - y), \tag{41}$$

where the reproductive number for resistant strains is unaffected by antibiotic treatment. For sensitive strains, antibiotic treatment reduces the probability of acquisition, b_p during treatment. Hence if q is the percentage reduction in b_p during treatment, $b_p(a) = (1 - a)b_p + a(1 - q)b_p = b_p(1 - aq)$. Therefore $R_0(a) = (1 - aq)R_0$ and resistant strains will have a selective advantage provided $R'_0 \geqslant R_0(a)$ or equivalently;

$$a \geqslant \frac{1 - R'_0/R_0}{q}. \tag{42}$$

Once this threshold is breached, resistance will increase logistically until fixation. If $y(0) = 1 - 1/R_0(a)$ is the initial endemic prevalence of colonization, and $f_0 \simeq 1/N_p$ (one resistant patient) then

$$T_{50} \simeq \frac{D_p \ln(N_p - 1)}{R'_0 - R_0(a)}. \tag{43}$$

As an example, if $R'_0 = R_0(0)$ in the absence of antibiotic therapy, then equation (42) is always satisfied and resistant strains will always have a selective advantage. Therefore, $R'_0 - R_0(a) = aqR_0$, implying that if antibiotic consumption is halved then the time to reach 50% resistance (T_{50}) will double.

(ii) *Multiple drug policies*

Introducing a second antibiotic (or class of antibiotics) provides a greater scope for the management of the evolution of drug resistance. Sensitive infections can be treated with a choice of drug, but more importantly patients with resistant organisms can also be treated effectively. If two drugs are in use then four possible resistance patterns are possible, sensitive (y_p), resistant to drug 1 (y'_p), resistant to drug 2 (y''_p) and resistant to both drugs (y'''_p). Increasing the number of antibiotics gives a maximum of 2^N resistance patterns for N drugs used. Retaining the constant population size and QSS approximations, the model for two antibiotics takes the form

$$\frac{dy_p}{dt} = \mu y_p(R_0(a_1, a_2)(1 - y)) - \mu(a_1\sigma_1 + a_2\sigma_2)y_p, \tag{44}$$

$$\frac{dy'_p}{dt} = \mu' y'_p(R'_0(a_2)(1 - y) - 1) + \mu a_1\sigma_1 y_p - \mu' a_2\sigma_2 y'_p, \tag{45}$$

$$\frac{dy''_p}{dt} = \mu'' y''_p(R''_0(a_1)(1 - y) - 1) + \mu a_2\sigma_2 y_p - \mu' a_1\sigma_1 y''_p, \tag{46}$$

$$\frac{dy'''_p}{dt} = \mu'''y'''_p(R'''_0(1-y)-1) + \mu''a_1\sigma_1 y''_p + \mu' a_2\sigma_2 y'_p, \quad (47)$$

where $y = y_p + y'_p + y''_p + y'''_p$, a_i denotes the consumption of drug i, σ_i the rate of acquired resistance and we have assumed that antibiotic treatement has no effect for patients with multiply resistant organisms. Competition for susceptibles $(1-y)$ means that the strain with the highest effective reproductive number will eventually dominate, i.e. $y(t) \to 1-1/\max(R_0(a_1,a_2),R'_0(a_2),R''_0(a_1),R'''_0)$. The overall selection balance will be determined by precisely how the two drugs are used and whether antibiotic resistance confers a reduced transmission success. If antibiotic treatment is 100% effective in reducing colonization (i.e. $q_i = 1$) then $R'_0(a_2) = R'_0(1-a_2)$ and $R''_0(a_1) = R''_0(1-a_1)$. The precise influence on $R_0(a_1,a_2)$ depends on how the drug is used. If a single drug treatment is used then $R_0(a_1,a_2) = R_0(1-a_1-a_2)$ with $a_1 + a_2 \leqslant 1$. If, however, multiple antibiotics are used $a_1 + a_2$ may be greater than unity and we take the maximal form $R_0(a_1,a_2) = R_0(1-\max(a_1,a_2))$.

Figure 9 shows examples of intervention drug use strategies. Sequential drug use, whilst retaining the second antibiotic solely for resistant infections provides a good method of retaining overall efficacy at the risk of multiple resistance. This policy is, however, determined by the rate of acquired resistance for each drug, the relative LOS for resistant patients and whether multiply resistant patients can be effectively isolated. The effectiveness of rotating antibiotics at regular intervals depends on the period of rotation; too frequent and resistance has no time to decline, too infrequent and resistance may reach endemic levels. It has been argued that the most efficient policy is to use multiple therapy for all patients (Bonhoeffer *et al*. 1997). This has the advantage that the risk of acquired resistance will be much lower (since singly resistant strains are removed and multiple resistance unlikely). However, this brings complications of cost and possible side effects. Provided multiply resistant patients can be effectively isolated (i.e. $R'''_0 \simeq 0$, e.g. by removal from the ICU), careful management of resistance is possible using both interventionist (e.g. cycling) and non-interventionist (e.g. combination) policies.

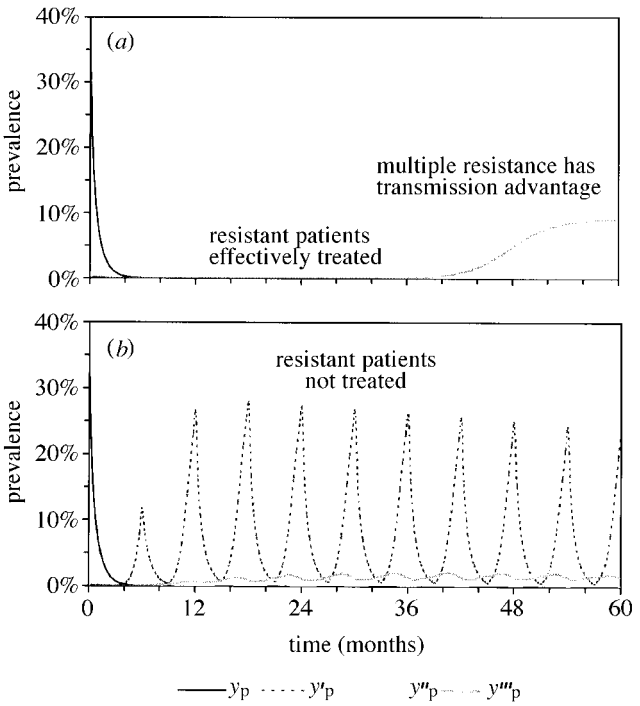

Figure 9. Emergence of multiple antibiotic resistance in an intensive care unit under (*a*) single antibiotic use in which resistant patients receive treatment with the second antibiotic, and (*b*) antibiotic rotation at regular, six-month intervals. Effective control of multiple resistance depends critically on the isolation of multiply resistant patients from transmission. Parameters used, $R_0 = R'_0 = R''_0 = 1.5$, $R'_0 = 1.1$, $D_p = 14$ days if multiply resistant and seven days otherwise, $a = 50\%$ of patient stay, $\sigma_1 = \sigma_2 = 1\%$. Prior to the introduction of therapy, colonization is assumed endemic and sensitive to both antibiotics.

4. EPIDEMIC SPREAD OF HOSPITAL OUTBREAKS OF MRSA AND VRE

(a) *Transmission model*

The rapid dissemination of multiply resistant strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) presents new challenges to the treatment of hospital-acquired infection. In England and Wales the number of hospitals affected by epidemic MRSA has increased from 40 per month in 1993 to more than 100 per month in 1997 (PHLS 1997). In New York City the transmission of VRE between hospitals led to 38 out of 81 hospitals reporting VRE outbreaks within three years (Frieden *et al*. 1993). The recent emergence of VRE in hospitals in the UK is of particular concern since vancomycin use is restricted to the treatment of MRSA and other multiply resistant infections. Nevertheless, epidemic strains of VRE were first detected in the UK in 1987, and as recently as 1995, were detected in 47 hospitals (including 27 for the first time) (PHLS 1996).

In many instances hospital outbreaks have proved both expensive (in associated costs) and difficult to eradicate, requiring careful surveillance and effective infection control measures (Cookson 1995; Boyce *et al*. 1995; Shay *et al*. 1995; Cox & Conquest 1997). Each case of MRSA in England and Wales was estimated to carry an additional cost of £2500 in increased patient stay and additional antimicrobial treatment (Mehtar 1995). The longer an outbreak persists, the greater the likelihood that it may spread between wards and eventually to other unaffected hospitals or into the community. Reductions in the duration of outbreaks and the transfer of colonized or infected patients are therefore of the utmost importance during the early stages of an epidemic, where greatest impact can be achieved.

Since epidemiological data on hospital outbreaks of VRE and MRSA are presently only available at a hospital level (rather than number of patients affected), we begin with an epidemiological framework in which hospitals are classified as either unaffected (susceptible) or having a confirmed outbreak (infectious). In the immediate period post-outbreak, a hospital may be on increased alert and less susceptible to subsequent outbreaks (recovered–immune), although such effects are likely to be small. Outbreaks arise as a consequence of either *de novo* spontaneous introduction, perhaps from a

background source such as a nursing home or the community, at a per capita rate σ, or by the transfer of colonized patients and staff between institutions. Once confirmed, an outbreak persists for an average duration D days, with eradication rate $\gamma = 1/D$. We assume that the total number of hospitals remains constant for the duration of the epidemic. If $n(t)$ denotes the number of affected hospitals at time, t, and N is the total number of hospitals, then $n(t)$ is determined by the differential equation

$$\frac{\mathrm{d}n(t)}{\mathrm{d}t} = \sigma(N - n) + \beta n(N - n) - \gamma n. \tag{48}$$

The transmission parameter, β, incorporates the prevalence of colonization in the source hospital, the transfer rate between hospitals and the probability of establishing an outbreak in the unaffected hospital. Equation (48) is the closed SIS model with immigration of infectives (see Appendix A) and can be rewritten in terms of two new parameters; growth rate, $r = \beta N - (\gamma + \sigma)$ and carrying capacity, $K = r/\beta$,

$$\frac{\mathrm{d}n(t)}{\mathrm{d}t} = \sigma N + rn(1 - n/K). \tag{49}$$

Data suggest that spontaneous outbreaks are rare for MRSA (PHLS 1997; Austin & Anderson 1999), and we take the limiting approximation $\sigma \to 0$, to obtain the well-known logistic solution

$$n(t) = \frac{Kn_0 \exp(r(t - t_0))}{n_0 \exp(r(t - t_0)) + K - n_0}. \tag{50}$$

It is helpful to make the transformation from ecological parameters, r and K, to epidemiological parameters, R_0 and D, where $R_0 = \beta ND$ is the number of secondary outbreaks generated by the first primary outbreak, such that $R_0 = N/(N - K)$ and $rD = K/(N - K)$.

Once an epidemic has begun to take off, stochastic fluctuations during the exponential phase are not very important. However, as the number of affected hospitals approaches the endemic state ($n^* = K$) fluctuations away from the endemic state become significant, and it is important to evaluate their magnitude (Appendix A).

Surveillance programmes and infection control practices can reduce both the transmission parameter β, and outbreak duration D. Fractional changes in these key parameters give corresponding changes in growth rate and carrying capacity such that,

$$\frac{\Delta r}{r} = \left(1 + \frac{1}{rD}\right)\frac{\Delta\beta}{\beta} + \frac{1}{rD}\frac{\Delta D}{D},$$
$$\frac{\Delta K}{K} = (N - K)\left(\frac{\Delta\beta}{\beta} + \frac{\Delta D}{D}\right). \tag{51}$$

Reductions in either transmission parameter or outbreak duration will therefore be equally effective in the long-term reduction in carrying capacity. However, reductions in transmission produce greater short-term reductions in growth rate and lower incidences of new outbreaks.

(b) *EMRSA-15 in England and Wales*

Epidemic strains of MRSA are colonizing hospital patients throughout England and Wales (PHLS 1997)

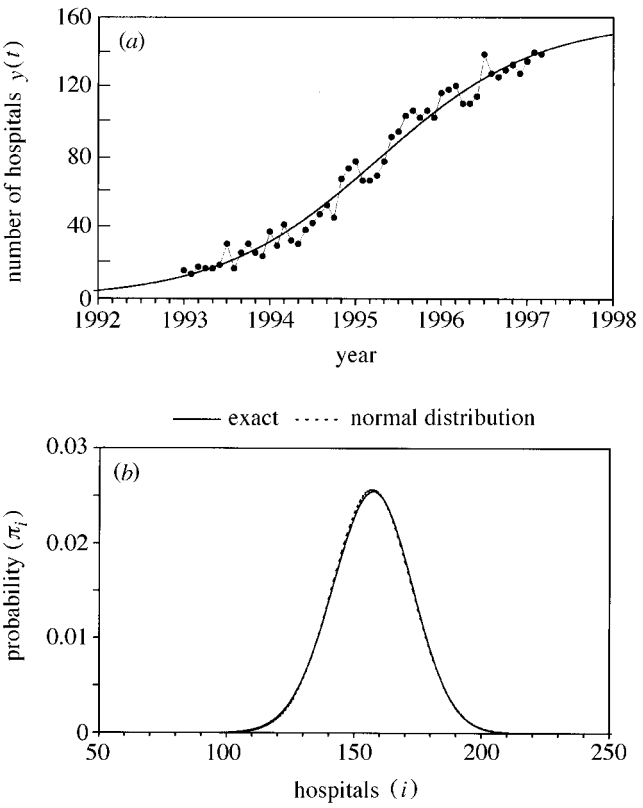

Figure 10. (*a*) Predicted and observed (PHLS 1997) number of EMRSA-15 outbreaks in England and Wales each month, 1992–1998. (*b*) Equilibrium probability distribution, π_i, that i hospitals will be affected. Exact results are in excellent agreement with the normal distribution approximation (see Appendix B).

(figure 10*a*). Strain EMRSA-15 has become widely disseminated and now accounts for over 100 affected hospitals per month. Assuming *de novo* introductions are infrequent ($\sigma \simeq 0$), maximum-likelihood techniques can be used to estimate the three unknown parameters; r, K and $n_0 = n(1993)$. Assuming a total of $N = 400$ hospitals are at risk, the log likelihood, l is given by

$$l(r,K,n_0) = \frac{1}{N}\sum_i n_i \log(n(t_i)/N + (N - n_i) \times \log(1 - n(t_i)/N), \tag{52}$$

$$\chi^2 = 2(l_{\mathrm{data}} - l(r,K,n_0)), \tag{53}$$

where n_i is the number of reported outbreaks at time t_i and i is summed over all available data points. Maximizing $l(r,K,n_0)$ gives $r = 1.08\,\mathrm{yr}^{-1}$ (95% CI 0.94–1.20), $K = 158$ hospitals (95% CI 143–173) and $n(1993) = 13.2$ (95% CI 10.8–15.6) hospitals ($\chi^2 = 42.34$, $\nu = 48$ d.f., $P = \Gamma(\frac{1}{2}\chi^2, \frac{1}{2}\nu)/\Gamma(\frac{1}{2}\nu) = 0.703$) (figure 10*a*). Converting to epidemiological parameters, $R_0 = 1.66$, with an average outbreak duration, $D = 219$ days. These results serve to highlight both the rapid spread and, more importantly, persistence of EMRSA-15. Once the endemic state is reached, stochastic fluctuations of up to ± 30 either side of K are predicted with fluctuation index $\sigma_K^2/\langle K\rangle = 1.54$ (figure 10*b*).

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

(c) *Model refinements*

(i) *Hospital size*

Heterogeneity in hospital size and organization may have considerable influence on the transmission dynamics. Subdividing hospitals by size, let N_k denote the total number of hospitals with k beds (k may denote a subclass) and n_k the number with outbreaks. Then $N = \sum_k N_k$ and the number of hospitals with k beds reporting outbreaks will be

$$\frac{\mathrm{d}n_k(t)}{\mathrm{d}t} = \sigma_k(N_k - n_k) + \lambda_k(N_k - n_k) - \gamma_k n_k, \tag{54}$$

where $\lambda_k = \sum_l \beta_{kl} h_l$ is the force of infection and β_{kl} the transmission parameter from a hospital with l beds to one with k beds. Assuming that λ_k scales with size (i.e. $\lambda_k = k\lambda$ or equivalently $\beta_{kl} = kl\beta/\langle k\rangle$) whilst outbreak duration D remains constant, at endemic equilibrium λ satisfies (Anderson & May 1991)

$$1 = \frac{1}{\langle k\rangle^2}\sum_l \frac{l^2 \beta K_l}{\gamma + l\lambda}. \tag{55}$$

The reproductive number $R_0(k)$ is obtained in the limit $\lambda \to 0$, hence

$$R_0(k) = \frac{\beta N D\langle k^2\rangle}{\langle k\rangle^2}. \tag{56}$$

The reproductive number can be significantly greater than the mean behaviour if the standard deviation $\sigma_k^2 = \langle k^2\rangle - \langle k\rangle^2$ is much greater than the mean $\langle k\rangle$. So-called 'superspreading hospitals' can therefore play a disproportionate role. For England and Wales hospitals are graded by NHS trust size (data not shown), rather than number of beds and are accurately described by a truncated normal distribution of the form

$$p(x) = \frac{\exp\left(-(x-\mu)^2/2\sigma^2\right)}{\sigma\sqrt{\pi/2}(1 + \mathrm{erf}(\mu/2\sigma))}, \tag{57}$$

where $p(x)$ is the probability a hospital will have x beds, $\mu = 432.5$ and $\sigma = 410.7$. The corresponding mean available beds per trust is $\bar{x} = 542.7$ with variance $\sigma_x^2 = \overline{x^2} - \bar{x}^2 = 108\,862$. Using this classification gives $R_0(k) = 1.39R_0$, if D remains constant or $R_0(k) = 2.32R_0$, if D also scales with trust size (Austin & Anderson 1999).

(ii) *Spatial spread*

The simple model of hospital–hospital transmission can be adapted spatially via either multiple patches (e.g. regional health authorities) (Lloyd & May 1996) or random diffusion (Shigesada & Kawasaki 1997). Let $n(\boldsymbol{x},t)$ denote the density of affected hospitals at time t and coordinate $\boldsymbol{x} = (x,y)$. The random diffusion model of epidemic spread in two dimensions is expressed as

$$\frac{\partial n(\boldsymbol{x},t)}{\partial t} = \sigma(N - n) + \beta n(N - n) - \gamma n + \Delta\nabla^2 n, \tag{58}$$

where Δ is the diffusion coefficient. Exact solution of this equation is not possible, although approximation of the exponentially growing phase with $\sigma = 0$ gives the radial solution

$$n(\rho,t) = \frac{n_0}{4\pi\Delta t}\exp\left(\frac{(R_0 - 1)t}{D} - \frac{\rho^2}{4\Delta t}\right), \tag{59}$$

at time t and distance ρ from the primary outbreak. The distribution at any given time is Gaussian, although the density increases exponentially at large time-scales. A wave of outbreaks will propagate from the primary hospital with limiting velocity

$$c = 2\sqrt{\frac{\Delta(R_0 - 1)}{D}}. \tag{60}$$

Our estimates of the growth rate for EMRSA-15 suggest that $c \simeq 2.1\sqrt{\Delta}$. Once more detailed information becomes available about the spatial spread of various EMRSA strains, theory may provide possible explanations of why different strains have had very different epidemic patterns, and how the present epidemic of VRE might spread throughout England and Wales.

5. ANTIBIOTIC RESISTANCE IN THE COMMUNITY

Although hospitals are rightly viewed as so-called 'hot zones' where selection of multiply resistant strains is most common, the bulk of antibiotic consumption occurs in the community. As already demonstrated, the primary selection pressure driving changes in the frequency of resistance is the volume of drug use. Establishing a precise quantitative relationship between antibiotic consumption and the frequency of resistance in community settings has been difficult due to the lack of longitudinal studies that record both resistance and consumption patterns (Nissinen *et al*. 1995; Arason *et al*. 1996; Seppälä *et al*. 1997). In a study by Nissinen *et al*. (1995) in Finland following the rapid emergence of β-lactamase resistance in *Moraxella catarrhalis*, increasing β-lactam consumption led to further increases in the frequency of β-lactamase producing clinical isolates. Many bacterial species, such as *Escherichia coli*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus*, exist as commensals in their human hosts with asymptomatic colonization. Arason *et al*. (1996) considered how the rates of carriage and resistance of *S. pneumoniae* in children in day-care centres were linked to antimicrobial consumption. Reductions in selection pressure will lead to reductions in resistance, although the time-scales may be considerable. In Finland, reducing macrolide consumption appears to have led to reductions in the frequency of macrolide resistance in *S. pyogenes* (Seppälä *et al*. 1997). Each of the studies has measured both antibiotic resistance and selection pressure, providing an opportunity to characterize the relationship between carriage, consumption and resistance.

(a) *A model of bacterial carriage and antibiotic consumption*

Few theoretical frameworks have examined the coupling between population genetics, transmission dynamics and antibiotic consumption (Austin *et al*. 1997, 1999; Levin *et al*. 1997). We begin by proposing a simple mathematical framework in which a population of human hosts experience colonization by a directly transmitted commensal organism (such as *S. pneumoniae* or *H. influenzae*). Antibiotic treatment is assumed to be prescribed independently of colonization in response to overt infection by

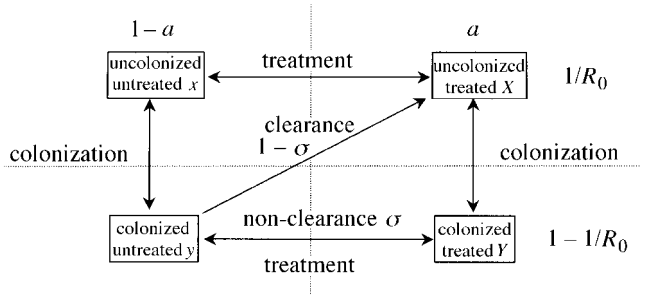

Figure 11. Mathematical framework for bacterial colonization by directly transmitted organisms incorporating the effects of antibiotic consumption. Antibiotics are prescribed to a proportion, a, of the population and are assumed to clear colonization in a proportion $(1-\sigma)$ of treated hosts (see text for equations).

other strains or species that induce morbidity. In the absence of 'resistant' strains (where resistance will be more clearly defined later), hosts fall into one of four classes; untreated-uncolonized (x), treated-uncolonized (X), untreated-colonized (y) and treated-colonized (Y) (figure 11). The prevalence of each of these classes is determined by the differential equations;

$$\frac{dx(t)}{dt} = \Lambda - \beta x(y+Y) - \alpha x + \gamma X + \lambda y - \mu x, \tag{61}$$

$$\frac{dy(t)}{dt} = \beta x(y+Y) - \alpha y + \gamma Y - (\lambda+\mu)y, \tag{62}$$

$$\frac{dX(t)}{dt} = \alpha(x+(1-\sigma)y) - \phi\beta X(y+Y) + \lambda Y - (\gamma X+\mu)X, \tag{63}$$

$$\frac{dY(t)}{dt} = \alpha\sigma y + \phi\beta X(y+Y) - (\gamma+\lambda+\mu)Y, \tag{64}$$

where α is the prescribing rate (per unit time), $1/\gamma$ the average length of treatment (typically days) and σ the probability that treatment does not clear colonization. The transmission dynamics of colonization are determined by β, the rate commensals are spread to other hosts, ϕ the protection afforded by treatment and $1/\lambda$ the average duration of colonization (typically months). Demographics are described by Λ, the per capita birth–immigration rate and $1/\mu$ the average duration hosts remain in the community. For children in day-care centres or the elderly in nursing homes $1/\mu$ may be comparable with $1/\lambda$. For analytical simplicity we assume that the number of hosts is fixed (i.e. $\Lambda = \mu$), hence $x+y+X+Y=1$ at all times. The basic reproductive number is given by $R_0 = \beta/\lambda'$, where $\lambda' = \lambda+\mu$. In the absence of antibiotic therapy, a commensal can cause an epidemic with probability $1-1/R_0$ and will become established with endemic prevalence $p = y^* = 1-1/R_0$.

(i) *Antibiotic consumption*

Consumption of antibiotics is conventionally measured in defined daily doses per 1000 adults (DDDs/1000), equivalent to the proportion of the community, $a = X+Y$, receiving treatment at any time. For adults, the equivalence is good and $a \simeq 0.5$–1%; however, for children, where doses depend on age and consumption is much greater ($a \simeq 5\%$), the equivalence is poor (Austin *et al.* 1999). For a constant population size, a is determined by

$$\frac{da(t)}{dt} = \alpha(1-a) - (\gamma+\mu)a, \tag{65}$$

which has the general solution

$$a(t) = \frac{\alpha}{\alpha+\gamma+\mu}(1-\exp(-(\alpha+\gamma+\mu)t)). \tag{66}$$

Since typical treatment times are short compared to colonization ($\gamma \gg \lambda$), a rapidly reaches the equilibrium value $a \simeq \alpha/\gamma$ or equivalently; prescribing rate multiplied by length of treatment. The simple assumptions about the nature of antibiotic treatment lead to two endemic extremes, depending on non-clearance rate, σ, and reduced susceptibility, ϕ.

(ii) *Antibiotic treatment clears and prevents colonization*

Where commensals are fully susceptible to antibiotics, treatment may both clear and prophylactically protect against colonization completely ($\phi = \sigma = 0$). Increasing antibiotic consumption will therefore reduce the average duration of colonization and the number of hosts who are susceptible. The prophylactic properties of treatment imply that the endemic state is given by

$$x^* = \frac{1}{R_0}\left(1+\frac{\delta a}{1-a}\right), \quad y^* = 1-a-x^*, \quad X^* = a, \quad Y^* = 0, \tag{67}$$

where $\delta = (\mu+\gamma)/(\mu+\lambda)$ is the ratio of length of colonization to length of treatment (typically $\delta \gg 1$). Eradication of a commensal from a population is possible provided $y^* \leqslant 0$, or equivalently $a \geqslant a_c(p)$ where p is the prevalence without treatment ($p = 1-1/R_0$), and the threshold consumption is given by

$$a_c(p) = \frac{1}{2}\left\{(p+1+\delta(1-p)) - \sqrt{(p+1+\delta(1-p))^2 - 4p}\right\}. \tag{68}$$

For example, when 50% of hosts are colonized and $\delta = 4$, a threshold $a_c = 15\%$ of hosts must be treated at any time (figure 12). Since a is typically much less than 100% and δ large, to $O(a)$,

$$a_c \simeq \frac{p}{1+\delta(1-p)} = \frac{R_0-1}{R_0+\delta}, \tag{69}$$

giving $a_c = 1/6$ for the previous estimate.

(c) *Antibiotic treatment has no effect on colonization*

Should antibiotic treatment leave colonization unchanged ($\phi = \sigma = 1$) (which may be the case where a commensal is fully resistant or an antibiotic has very high specificity and does not reach the colonization site), there is an absolute separation between consumption and carriage such that

$$x^* = (1-a)/R_0, \quad y^* = (1-a)(1-1/R_0), \quad X^* = a/R_0, \quad Y^* = a(1-1/R_0). \tag{70}$$

Where antibiotic consumption is low, treated-colonized hosts (Y) always form a very small fraction of the whole

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

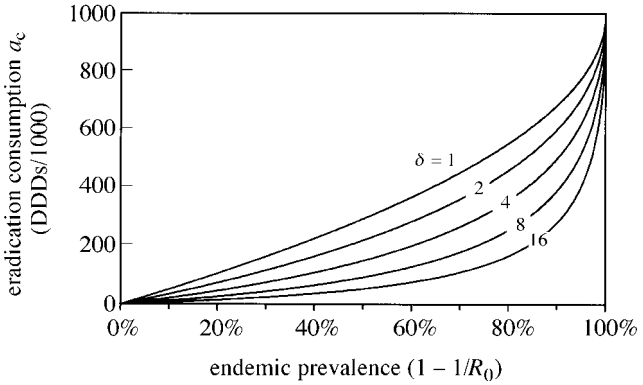

Figure 12. Eradication threshold consumption, a_c as a function of endemic colonization prevalence and ratio of duration of colonization to duration of treatment, δ, assuming antibiotic treatment clears and prevents colonization. Highly prevalence commensals require extensive treatment rates for elimination.

and their contribution to transmission can in most instances be ignored.

The true effect of antibiotic treatment is likely to lie between these two extremes. When a new antibiotic is first introduced, $\sigma \simeq 0$, implying that treatment will have a considerable effect on carriage. As the frequency of resistance increases so too will σ, eventually tending to unity when resistance is complete. To incorporate the effects of resistance three possibilities can be considered. First, a mean minimum inhibitory concentration (MIC) can be defined over the whole population. The clearance failure rate must evidently be a function of MIC; low MICs will lead to clearance, high MIC non-clearance. Resistance is classically determined by break points, with the broad distinctions; (S)ensitive, (I)ntermediate or (R)esistant being made. Second, using microsimulation techniques, a population-genetic approach can be used to model the effects of individual hosts. Competing selection takes place within colonized hosts, and the relative fitness of sensitive and resistant strains will be determined by whether individual hosts are receiving treatment (Levin *et al*. 1997). Finally additional resistant classes can be added to the original framework to include untreated-resistant and treated-resistant colonized hosts (Austin *et al*. 1997*b*).

(b) *Non-clearance as a function of MIC*

We have already seen how the MIC plays an important role in determining the within-host outcome of antibiotic therapy. Where doses maintain antibiotic concentrations above MIC for sufficient periods, clearance of bacteria will result. For commensal organisms, which may colonize other areas of the body aside from the pathogen of interest, the MIC antibiotic concentration may be different but the underlying criterion remains. The rate of non-clearance is therefore a function of mean MIC (i.e. $\sigma(m)$). Since antibiotic activity is well described by the $E_{\max}$ model, the non-clearance rate will also be determined by a saturating function of the form

$$\sigma(m) = \frac{m^n}{m^n + m_{50}^n}, \tag{71}$$

where m_{50} is the MIC at which only 50% of colonization is cleared and n is a constant determined by the underlying within host pharmacodynamics. If a partial differential equation approach is taken, x, y, X and Y become functions of both time and MIC, such that equations (61)–(64) are replaced by equations of the form

$$\begin{aligned} \frac{\partial x(m,t)}{\partial t} + \frac{\partial x(m,t)}{\partial m}\frac{dm}{dt} &= \Lambda - \beta(m)x(y+Y) \\ &\quad - \alpha x + \gamma X + \lambda(m)y - \mu x, \\ \vdots \qquad & \vdots \qquad\qquad \vdots \end{aligned} \tag{72}$$

where parameters β, λ, σ and ϕ become functions of m. The mean MIC is given by

$$\langle m(t) \rangle = \frac{\int_0^\infty dm' m'(y(m',t) + Y(m',t))}{\int_0^\infty dm'(y(m',t) + Y(m',t))}, \tag{73}$$

and the frequency of resistance takes the form

$$f(m_r) = \frac{\int_{m_r}^\infty dm'(y(m',t) + Y(m',t))}{\int_0^\infty dm'(y(m',t) + Y(m',t))}, \tag{74}$$

where m_r is the breakpoint MIC determining resistance. Evolution of the partial differential equation system is determined by the dynamics of the MIC, dm/dt. When antibiotic treatment does not clear colonization, but instead selects pre-existing bacteria with increased MIC (so-called acquired resistance), the mean MIC will increase. Any increase must, however, be density-dependent because when the MIC is very large, incremental changes in MIC following treatment failure will be negligible. Increasing MIC may carry additional metabolic costs (i.e. reduced fitness) and therefore withdrawal of selection may cause a reversal of MIC with some characteristic time-scale. The rate MIC increases is dependent on the number of hosts who select for increased MIC hence

$$\frac{dm}{dt} = \mathcal{F}(m) \int_0^\infty dm' \sigma(m') \alpha(t) y(m',t), \tag{75}$$

where $\mathcal{F}(m)$ is a monotonically decreasing function of MIC which incorporates the fact that the increase in m becomes smaller as m becomes large.

Rather than solve the full equations, we make the limiting assumption that only σ is a function of m, and that m describes the mean MIC in the population as a whole. The principal limitation of this assumption is that all information about the frequency of antibiotic resistance is lost. Equations (61)–(64) remain unchanged with the addition of a further equation for m of the form

$$\frac{dm}{dt} = \mathcal{F}(m) \frac{\alpha m^n y(t)}{m^n + m_{50}^n}. \tag{76}$$

The system of equations exhibits limiting behaviour when $m \ll m_{50}$ and $m \gg m_{50}$, i.e. $\sigma \simeq m/m_{50}$ and $\sigma \simeq 1$, respectively. Immediately after an antibiotic has been introduced $y(0) = y^*(a)$ (equation (68)) and any density-dependent effects on MIC increase will be small. If $n = 1$, $m(t)$ takes the exponential form

$$m(t) \simeq m_0 \exp(\mathcal{F}(m_0) y^*(a) \alpha t / m_{50}) \tag{77}$$

with an MIC doubling time, τ_m of

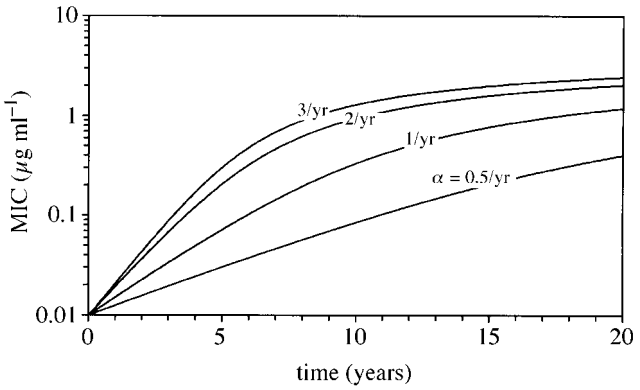

Figure 13. Increasing MIC for *Streptococcus pneumoniae* over time as a function of antibiotic treatment courses per year. Parameters used are given in the text. The MIC doubling time is approximately two years if 1.4% of host receive antibiotic treatment at any time ($\alpha = 1\,\mathrm{yr}^{-1}$).

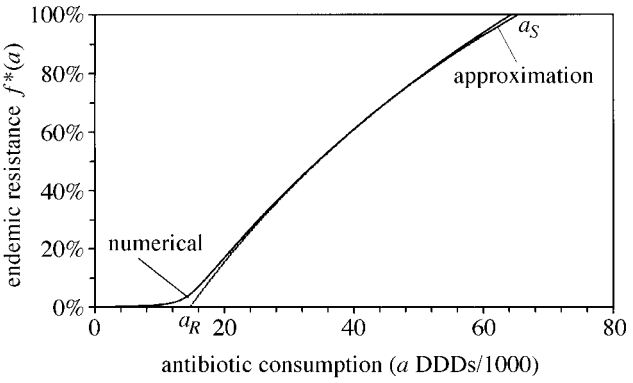

Figure 14. Endemic frequency of resistance, $f^*(a)$ as a function of antibiotic consumption, a. In the absence of non-clearance ($\sigma = 0$) two thresholds are defined, $a_{\mathcal{Z}}$ for the emergence of resistance and a_y for the eradication of sensitive strains. Parameters used are $R_0 = 2$, $R_0' = 2.6$, $\phi = 0.43$, $1/\lambda = 1/\lambda' = 1.1$ months and $1/\mu = 72$ months. Numerical solution shows the effect of treatment failure when $\sigma = 10^{-2}$.

$$\tau_m = \frac{m_{50}\log 2}{\mathcal{F}(m_0)y^*(a)\alpha}. \tag{78}$$

Communities with higher colonization rates or antibiotic consumption, will see faster emergence of strains with elevated MICs. Once MICs are above m_{50} non-clearance becomes much more frequent. It is here that density-dependent effects may be more clearly felt. Where there is no effect, $m(t)$ increases linearly with time. When $\mathcal{F}(m)$ decreases monotonically, an eventual upper bound is placed on m.

Numerical solutions with parameter estimates typical of penicillin-resistant *Streptococcus pneumoniae* (PRP); $R_0 = 2$, $1/\lambda = 2$ months (Christenson *et al.* 1997), $\alpha = 1\,\mathrm{yr}^{-1}$, $1/\gamma = 5$ days ($a = 1.4\%$), $m_{50} = 1\,\mu\mathrm{g\,ml}^{-1}$, $\mathcal{F}(m) = 1\,\mu\mathrm{g\,ml}^{-1}$ give a doubling time of approximately two years (figure 13). Exact calculation of $\mathcal{F}(m)$ requires detailed longitudinal MIC data which has yet to be made available. Resistant strains of *S. pneumoniae* are characterized by MIC in excess of $1\,\mu\mathrm{g\,ml}^{-1}$, suggesting that if $m(0) = m_{50}/100$, PRP carriage will become a problem after 10–20 years of relatively intense selection.

(c) *Explicit resistant classes*

A second way of incorporating resistance is via the introduction of an explicit second commensal strain, which is assumed to either be resistant or at the very least have reduced susceptibility (Austin *et al.* 1997, 1999*a*). A further two classes of host are required: untreated-resistant (z) and treated-resistant ($\mathcal{Z}$). Since antibiotic treatment is assumed to either clear sensitive strains or induce acquired resistance (with probability σ), the class that is treated-sensitive (Y) is redundant. Resistance is again assumed to be associated with some fitness cost, although the precise nature of this cost is in the form of reduced transmission success (measured by R_0'). Recalling that the reproductive number is the product of transmission rate and duration of carriage, resistant strains may manifest themselves either via reduced transmissibility (lower β) or increased duration of carriage (higher λ), or both. A further measure of transmission success is captured in the role of superinfection, i.e. the net probability that a host colonized with a resistant strain will revert to sensitive following contact with other sensitively colonized hosts. Under these assumptions, the two-strain model with antibiotic prescribing takes the form

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = \Lambda - \beta xy - \beta' x\mathcal{Z} - \alpha x + \gamma X + \lambda y + \lambda' z - \mu x, \tag{79}$$

$$\frac{\mathrm{d}y(t)}{\mathrm{d}t} = \beta xy + \phi\beta yz - (\alpha + \lambda + \mu)y, \tag{80}$$

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = \beta' x\mathcal{Z} - \phi\beta yz - (\alpha + \lambda' + \mu)z + \gamma\mathcal{Z}, \tag{81}$$

$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = \alpha(x + (1-\sigma)y) - \phi\beta X\mathcal{Z} + \lambda'\mathcal{Z} - (\gamma + \mu)X, \tag{82}$$

$$\frac{\mathrm{d}\mathcal{Z}(t)}{\mathrm{d}t} = \alpha(z + \sigma y) + \phi\beta X\mathcal{Z} - (\gamma + \lambda' + \mu)\mathcal{Z}, \tag{83}$$

where $\mathcal{Z} = z + \mathcal{Z}$ and primes denote parameters for resistant commensal strains. In the absence of resistance endemic colonization is again given by equation (68), with the threshold for eradication a_c, unchanged.

(i) *Relationship between antibiotic consumption and resistance*

Using the simplifying assumption that antibiotic consumption is low ($a \ll 1$), an approximate solution of the model is possible (Appendix B). If non-clearance rates are zero, two thresholds are defined; $a_{\mathcal{Z}}$ for emergence of resistance, and a_y for the eradication of sensitive commensal (equivalent to a_c). Coexistence requires only that $a_{\mathcal{Z}} \leqslant a \leqslant a_y$. Where there is no transmission fitness cost ($R_0' = R_0$), $a_y = \phi a_c$ and $a_{\mathcal{Z}} = a_y/(1+\phi)$ (figure 14). The endemic frequency of resistance, $f^*(a)$, is related to antibiotic consumption by the relationship

$$f^*(a) = \frac{1 - a_{\mathcal{Z}}/a}{1 - a_{\mathcal{Z}}/a_y}. \tag{84}$$

Changes in antibiotic consumption, Δa, will give corresponding changes in resistance, $\Delta f^*(a)$, such that

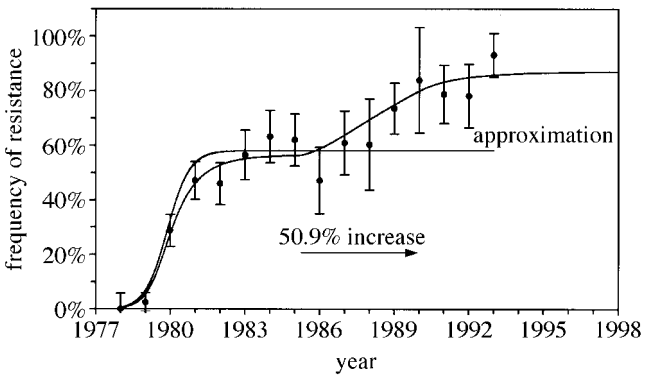

Figure 15. Prediction of a two-step rise in the frequency of β-lactamase producing isolates of *Moraxella catarrhalis* (Nissinen *et al*. 1995). Initial colonization is assumed to be endemic with $\mathcal{Z}(0) = 0.002$ and $a = 37.7$ DDDs/1000 children (4%). All other parameters are as in figure 15. The approximate solution (Appendix B) is in good agreement with the numerical results prior to the introduction of cephalosporins in 1986.

$$\frac{\Delta f^*(a)}{f^*(a)} = \frac{a_{\mathcal{Z}}}{a - a_{\mathcal{Z}}} \frac{\Delta a}{a}, \tag{85}$$

with limits $\Delta a/a = (a_y - a)/a_y$ for the fixation of resistance and $\Delta a/a = (a_{\mathcal{Z}} - a)/a$ for its eradication. Small changes in antibiotic consumption can therefore induce considerable changes in resistance if consumption is sufficiently close to either of the thresholds, $a_{\mathcal{Z}}$ or a_y.

(ii) *Emergence of β-lactamase resistance in* Moraxella catarrhalis *in Finland*

Since 1977 *M. catarrhalis* resistance to β-lactams has increased rapidly in Europe and the USA reaching 80–85% (Berk *et al*. 1996). Studies in Finland using clinical isolates from otitis media in children aged less than six years show a rapid rise in resistance from 0% ($n = 53$) in 1978 to 57% ($n = 115$) in 1983. During this time β-lactam antibiotic consumption was estimated to have remained roughly constant at 5.5 DDDs/1000 adults ($a = 0.55\%$) (Nissinen *et al*. 1995). After the introduction of second generation cephalosporins there followed a further 51% increase in β-lactam consumption and an associated rise in β-lactam resistance (figure 15). Parameter estimation is done by minimizing a weighted least squares estimate using multidimensional direction set methods (Press *et al*. 1992) and numerical realizations of the equations (79)–(83). The approximate solution gives excellent agreement where selection pressure is constant (1978–1985).

Parameter estimates give $a = 3.8\%$ or equivalently 38 DDDs/1000 children, which is in keeping with other estimates of infant antibiotic consumption (Arason *et al*. 1996). It should be stressed that the parameters are for children less than six years old and that evidently antibiotic consumption in children differs widely from that of the whole community. This non-equivalence presents an important gap in our knowledge. Since children are the largest consumers of antibiotics, conventional measures of consumption fail to estimate the true selection pressure in those with the highest rates of carriage. There is an interplay between transmission success (R_0'/R_0) and superinfection. Resistant strains may have higher transmission success ($R_0' \geqslant R_0$) but be susceptible to superinfection by sensitive strains ($\phi > 0$).

6. DISCUSSION

The series of problems discussed in this paper are broad, ranging from MIC levels within a treated patient to the community-based frequency of drug resistance. In each case mathematical models provide insights into the interpretation of observed pattern and the management of antibiotic resistance. The various models discussed reflect differing degrees of sophistication in terms of the overall goal of melding approaches from pharmacology, microbiology, population genetics and epidemiology. By concentrating first on the within-host dynamics of treatment and expanding into population-based epidemiological models, it is possible to see how the the treatment of the individual has implications for the wider population.

Our analyses demonstrate clearly the widely differing proximity of theory with experiment and observation. In some cases, such as the spread and management of antibiotic resistance in an intensive care setting, estimates for the values of key parameters and variables are often available. In other areas, such as the pharmacodynamics of the interaction between specific drugs and specific bacteria, data are sparse (particularly so for resistant organisms). It is surprising that the level of quantification is so high for the pharmacokinetic side, yet so sparse for the pharmacodynamics. Models should help to stress how important such measurements are to the evaluation and management of antibiotic resistance. Specifically, where one or more drugs are used to treat a particular bacterial infection, the design of treatment protocols to minimize the likelihood of the emergence of resistance requires much more precise pharmacodynamic data.

More generally, there are also important gaps in quantification and measurement in the population genetic and epidemiological areas. It again seems surprising that so few studies have provided precise longitudinal data on the frequency of resistance in a well-defined sample of the patient population, and concomittently, the volume of drug consumption over time in that population. The latter is the strength of selection and its precise measurement is key to the interpretation of how the frequency of resistance changes over time. Related to this issue is the question of sampling. In general, too little thought has been given to date on how best to monitor temporal changes in the frequency of resistance to a particular drug in defined organisms. There is an urgent need for concerted action internationally in this area, given the globally mixing nature of the world's population today and the speed with which antibiotic resistance can spread from one country to another.

Once data are available, the use of mathematical models provides a quantitative tool for possible scenario analysis. An obvious example is the epidemiological spread of multiply resistant bacteria between hospitals. Once the key parameters have been estimated, questions regarding the impact of intervention strategies (such as surveillance and outbreak control) can be addressed in a meaningful way. Understanding the dynamics of the model provides additional information regarding implementation time-scales. For example, theory demonstates

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

that the emergence time-scales for antibiotic resistance will be much greater than that required for decline.

The gaps in data needs are of obvious importance in the development of a robust theoretical framework and all efforts should be made to increase awareness of their existence. Indeed, one of the key roles of mathematical model development in infectious disease research is the identification of what needs to be measured to further understanding and better organize control interventions. In the field of antibiotic resistance, theory will certainly fill this role. However, it is important to recognize that even in the absence of a good observational database, theory also helps to interpret observed pattern, facilitate the development of better management practices and create a template for interdisciplinary research. The latter is of particular importance in developing an understanding of how best to slow the evolution and spread of antibiotic resistant organisms.

D.J.A. and R.M.A. acknowledge the Wellcome Trust for ongoing financial support. Correspondence and requests for materials to D.J.A. (daren.austin@zoology.ox.ac.uk).

APPENDIX A

(a) *SIS with immigration*

If a is the immigration rate of new infectives, the closed SIS model takes the form

$$\frac{\mathrm{d}n(t)}{\mathrm{d}t} = a + \mu R_0(\mathcal{N} - n)n/\mathcal{N} - \mu n, \tag{86}$$

or equivalently

$$\frac{\mathrm{d}n(t)}{\mathrm{d}t} = a + rn - sn^2, \tag{87}$$

with growth rate $r = \mu(R_0 - 1)$ and carrying capacity $K = \mathcal{N}(1 - 1/R_0) = r/s$. Completing the square and factorizing,

$$\frac{\mathrm{d}n(t)}{\mathrm{d}t} = s(\tfrac{1}{2}K(1+\phi) - (n - \tfrac{1}{2}K))(\tfrac{1}{2}K(1+\phi) + (n - \tfrac{1}{2}K)), \tag{88}$$

where

$$1 + \phi = \sqrt{1 + \frac{4a}{rK}}. \tag{89}$$

With a change of variables, $u(t) = n(t) - \frac{1}{2}K$ and $v = \frac{1}{2}K(1+\phi)$, the general solution is

$$\log\left(\frac{v + u(t)}{v - u(t)}\right) = \log\left(\frac{v + u(t_0)}{v - u(t_0)}\right) + r(1+\phi)(t - t_0). \tag{90}$$

Hence the final solution in terms of $n(t)$ is obtained by rearranging

$$\begin{aligned} n(t) = [&(K + \delta K)(n_0 + \delta K)\exp(r(1+\phi)(t - t_0)) \\ &- \delta K(K + \delta K - n_0)]/[(n_0 + \delta K) \\ &\times \exp(r(1+\phi)(t - t_0)) + K + \delta K - n_0], \end{aligned} \tag{91}$$

where $\delta K = \frac{1}{2}\phi K$. In the limiting case where immigration rates are much smaller than transmission (i.e. $4a \ll rK$),

$$\frac{\delta K}{K} \simeq \frac{a}{rK}, \qquad \frac{\delta r}{r} = 2\frac{\delta K}{K}. \tag{92}$$

(b) *Stochastic SIS model without immigration*

Setting $a = 0$, the stochastic version of the SIS model can be written in terms of a probability equation for $p_i(t)$, the probability that $n(t) = i$, such that

$$\begin{aligned} \frac{\mathrm{d}p_i(t)}{\mu \mathrm{d}t} =& (i+1)p_{i+1}(t) + (R_0 i(1 - i/\mathcal{N}) - i)p_i(t) \\ &- R_0(i-1)(1 - (i-1)/\mathcal{N})p_{i-1}(t). \end{aligned} \tag{93}$$

The quasi-equilibrium probabilities, ϕ_i can be obtained after setting $\mathrm{d}p_i/\mathrm{d}t = 0$, hence after rearrangement

$$(i+1)\pi_{i+1} + R_0 i(1 - i/\mathcal{N})\pi_i = i\pi_i + R_0(i-1)(1 - (i-1)/\mathcal{N})\pi_{i-1}. \tag{94}$$

Solution of this difference equation gives

$$\pi_i = \frac{q_i}{\sum_j q_j}, \quad q_{i+1} = \frac{R_0 i(i - i/\mathcal{N})}{i+1} q_i, \quad q_1 = \frac{1}{\mu}. \tag{95}$$

The average time to extinction from an initial state, i, $\tau_E(i)$ is approximately (Renshaw 1991) $\tau_E \simeq \sum_j q_j$, and for a pure logistic process (birth rate $= rn$, death rate $= rn^2/K$), $\tau_E \simeq \exp(K)/rK$, with stability index $\xi = \log(\tau_E) \simeq K$.

The quasi-equilibrium distribution, π_i can be approximated by both normal and negative binomial distributions with stochastic mean, $\langle K \rangle$, and variance, σ_K^2,

$$\langle K \rangle = \mathcal{N}\left(1 - \frac{1}{R_0}\right) - \frac{1}{R_0 - 1}, \qquad \sigma_K = \frac{\mathcal{N}}{R_0} \tag{96}$$

(see Renshaw (1991), chapter 3 for further details). The magnitude of fluctuations is determined by $\sigma_K^2/\langle K \rangle$. If $1 < R_0 < 2$, the variance will be greater than the mean and fluctuations considerable. Using the normal distribution approximation for π_i, the 95% confidence region for the endemic prevalence $k^* = K/\mathcal{N}$ is predicted to lie in the range

$$k^* \simeq 1 - \frac{1}{R_0} - \frac{1}{\mathcal{N}(R_0 - 1)} \pm \frac{1.96}{\sqrt{R_0 \mathcal{N}}}. \tag{97}$$

Therefore large population sizes and high transmission tend to reduce fluctuations in prevalence, whereas small numbers (e.g. ICUs) may be subject to very large fluctuations. Generalization of the transition region $R_0 \to 1$ has been done by incorporating a reflecting state at rather than the absorbing state p_0 (Nasell 1997). This is perhaps more characteristic of the case where immigration of new infectives is important.

APPENDIX B. APPROXIMATE SOLUTION OF ANTIBIOTIC CARRIAGE MODEL WITH RESISTANT CLASSES

If antibiotic consumption is low ($a \ll 1$) and the number of hosts remains constant, then $z(t) \simeq (1-a)\mathcal{Z}(t)$ and equations (79)–(83) simplify giving

$$\mathrm{d}y/\mathrm{d}t = \beta y\{y_0(a) - (1-a)(1-\phi)\mathcal{Z} - y\}, \tag{98}$$

$$d\mathcal{Z}/dt = \beta'\mathcal{Z}\{(1-1/R_0')-y(1+\phi'(1-a))-\mathcal{Z}\}+\sigma a y\gamma, \quad (99)$$

where $\phi\beta = \phi'\beta'$ and $y_0(a)$, is the endemic colonization prevalence in the absence of treatment, equation (67). Non-clearance ($\sigma \neq 0$) can maintain resistant commensals at a frequency $O(\sigma)$ even where there is considerable transmission fitness cost. The full coexisting endemic state, $(y^*,\mathcal{Z}^*)$ when $\sigma = 0$, is given by

$$\begin{aligned} y^*(a) &= \frac{y_0(a) - (1-a)(1-\phi)(1-1/R_0)}{1-(1-a)(1-\phi)(1+\phi'(1-a))}, \\ \mathcal{Z}^* &= 1 - \frac{1}{R_0'} - y^*(a)(1+\phi'(1-a)). \end{aligned} \quad (100)$$

Coexistence requires $y_0(a) \geqslant (1-a)(1-\phi)(1-1/R_0')$ or equivalently $a_{\mathcal{Z}} \leqslant a \leqslant a_y$, where in the absence of any cost of resistance ($R_0' = R_0$),

$$a_y = \phi a_c, \qquad a_{\mathcal{Z}} = \frac{\phi a_c}{1+\phi}. \quad (101)$$

Using the quasi-steady state approximation (QSSA), $dy/dt \simeq 0$, gives the relationship $y(\mathcal{Z}) \simeq y_0 - \mathcal{Z}(1-a) \times (1-\phi)$, which after substitution reduces equation (99) to a logistic equation with general solution

$$\mathcal{Z}(t) = \frac{\mathcal{A}(a)\mathcal{Z}_0 \exp(\mathcal{A}(a)(t-t_0))}{\mathcal{A}(a) + \mathcal{B}(a)\mathcal{Z}_0(\exp(\mathcal{A}(a)(t-t_0)) - 1)}, \quad (102)$$

where $\mathcal{A}(a) = \beta'[1 - 1/R_0' - y_0(a)(1+\phi'(1-a))]$ and $\mathcal{B}(a) = \beta'[1-(1-a)(1-\phi)(1+\phi'(1-a))]$. Hence the frequency of resistance $f(t,a)$ is given by

$$\begin{aligned} f(t,a) = {} & [\mathcal{A}(a)\mathcal{Z}_0 \exp(\mathcal{A}(a)(t-t_0))] \\ & /\{\phi\mathcal{A}(a)\mathcal{Z}_0 \exp(\mathcal{A}(a)(t-t_0)) + y_0(a) \\ & \times [\mathcal{A}(a) + \mathcal{B}(a)\mathcal{Z}_0(\exp(\mathcal{A}(a)(t-t_0)) - 1)]\}. \end{aligned} \quad (103)$$

For emergence, typically a single host is initially colonized (i.e. $\mathcal{Z}_0 \simeq 1/\mathcal{N}_{\text{hosts}}$). If there is no transmission fitness cost of resistance, the time to reach 50% resistance, τ_{50} is

$$\tau_{50} = \frac{1}{\beta\phi^2\mathcal{Z}^*(a)} \log \frac{y_0(a)\mathcal{Z}^*(a)\mathcal{N}_{\text{hosts}}}{\mathcal{Z}^*(a)(2-\phi) - y_0(a)}, \quad (104)$$

where $\mathcal{Z}^*(a) = \mathcal{A}(a)/\mathcal{B}(a)$. In the limit as $t \to \infty$, the endemic frequency of resistance, $f^*(a)$, takes the simple form

$$\begin{aligned} f^*(a) &= \frac{\mathcal{A}(a)}{\phi\mathcal{A}(a) + y_0(a)\mathcal{B}(a)} \\ &= \frac{(a-a_{\mathcal{Z}})}{(a-a_{\mathcal{Z}}) + a_{\mathcal{Z}}\dfrac{\phi R_0(R_0'-1) + (R_0-R_0')}{\phi' R_0'(R_0-1) + (R_0-R_0')}(1-a/a_y)}, \end{aligned} \quad (105)$$

provided antibiotic consumption lies in the range $a_{\mathcal{Z}} \leqslant a \leqslant a_y$.

REFERENCES

Aeschlimann, J. R., Zervos, M. J. & Rybak, M. J. 1998 Treatment of vancomycin-resistant *Enterococcus faecium* with RP 59500 (Quiupristin-Dalfopristin) administered by intermittent or continuous infusion, alone or in combination with doxycycline, in an *in vitro* pharmacodynamic infection model with simulated endocardial vegetations. *Antimicrob. Agents Chemother.* **42**, 2710–2717.

Albert, R. K. & Condie, F. 1981 Hand-washing patterns in medical intensive-care units. *New Engl. J. Med.* **304**, 1465–1468.

Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans: dynamics and control*. Oxford University Press.

Arason, V. A., Kristinsson, K. G., Sigurdsson, J. A., Stefánsdóttir, G., Mölstad, S. & Gudmundsson, S. 1996 Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *Br. Med. J.* **313**, 387–391.

Austin, D. J. & Anderson, R. M. 1999 The transmission dynamics of epidemic methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in England and Wales. *J. Infect. Dis.* (In the press.)

Austin, D. J., Kakehashi, M. & Anderson, R. M. 1997 The transmision dynamics of antibiotic-resistant bacteria: the relationship between resistance in commensal organisms and antibiotic consumption. *Proc. R. Soc. Lond.* B **264**, 1629–1638.

Austin, D. J., Bonten, M. J. N., Slaughter, S., Weinstein, R. A. & Anderson, R. M. 1998*a* Vancomycin-resistant enterococci in intensive care hospital settings, persistence, dynamics and the impact of infection control measures. *Proc. Natl Acad. Sci. USA*. (Submitted.)

Austin, D. J., White, N. J. & Anderson, R. M. 1998*b* The dynamics of drug action on the within-host population growth of infectious agents: melding pharmacokinetics with pathogen population dynamics. *J. Theor. Biol.* **194**, 313–339.

Austin, D. J., Kristinsson, K. G. & Anderson, R. M. 1999 The relationship between the volume of drug consumption in human communities and the frequency of antibiotic resistance. *Proc. Natl Acad. Sci. USA* **96**, 1152–1156.

Berg, P. H., Voit, E. O. & White, R. L. 1996 A pharmacodynamic model for the action of the antibiotic Imipenem on *Pseudomonas aeruginosa* populations in vitro. *Bull. Math. Biol.* **58**, 923–938.

Berk, S. L., Kalbfleisch, J. H. & The Alexander Project Collaborative Group 1996 Antibiotic susceptibility patterns of community-aquired isolates of *Moraxella catarrhalis* in Western Europe and in the USA. *J. Antimicrob. Chemother.* **38**(Suppl. A), 85–96.

Björkmann, J., Hughes, D. & Andersson, D. I. 1998 Virulence of antibiotic-resistant *Salmonella typhimurium*. *Proc. Natl Acad. Sci. USA* **95**, 3949–3953.

Blower, S. M., Porco, T. C. & Darby, G. 1998 Predicting and preventing the emergence of drug resistance in HSV 2. *Nature Med.* **4**, 573–578.

Bonhoeffer, S., May, R. M., Shaw, G. M. & Nowak, M. A. 1996 Virus dynamics and drug treatment. *Proc. Natl Acad. Sci. USA* **93**, 4398–4402.

Bonhoeffer, S., Lipsitch, M. & Levin, B. R. 1997 Evaluating treatment protocols to prevent antibiotic resistance. *Proc. Natl Acad. Sci. USA* **94**, 12 106–12 111.

Bonten, M. J., Hayden, M. K., Nathan, C., Van Voorhis, J., Matushek, M., Slaughter, S., Rice, T. & Weinstein, R. A. 1996 Epidemiology of colonization of patients and environment with vancomycin-resistant enterococci. *Lancet* **348**, 1615–1619.

Boyce, J. M., Mermel, L. A., Zervos, M. J., Rice, L. B., Potter-Bynoe, G., Giorgio, C. & Medeiros, A. A. 1995 Controlling vancomycin-resistant enterococci. *Infect. Control Hosp. Epidemiol.* **16**, 634–637.

Christenson, B., Sylvan, S. L. V. & Noreen, B. 1997 Carriage of multiresistant *Streptococcus pneumoniae* among children attending day-care centres in the Stockholm area. *Scand. J. Infect. Dis.* **29**, 555–558.

Cole, S. T. (and 41 others) 1998 Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature* **393**, 537–544.

Cookson, B. 1995 Aspects of the epidemiology of MRSA in Europe. *J. Chemother.* **7** (Suppl. 3), 93–98.

Cox, R. A. & Conquest, C. 1997 Strategies for the management of healthcare staff colonized with epidemic methicillin-resistant *Staphylococcus aureus*. *J. Hosp. Infect.* **35**, 117–27.

Doebbelling, B. N., Stanley, G. L., Sheetz, C. T., Pfaller, M. A., Houston, A. K., Annis, L., Li, N. & Wenzel, R. P. 1992 Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive-care units. *New Engl. J. Med.* **327**, 88–93.

Drusano, G. L., Jordan, D. E., Rosen, M. & Standiford, H. C. 1993 Pharmacodynamics of a fluoroquinolone antimicrobial agent in a neutropenic rat model. *Antimicrob. Agents Chemother.* **37**, 483–490.

Frieden, T. R., Munsiff, S. S., Low, D. E., Willey, B. M., Williams, G., Faur, Y., Eisner, W., Warren, S. & Kreisworth, B. 1993 Emergence of vancomycin-resistant enterococci in New York City. *Lancet* **342**, 76–79.

Hiramatsu, K., Aritake, N., Hanaki, H., Kawasaki, S., Hosoda, Y., Hori, S., Fukuchi, Y. & Kobayshi, I. 1997 Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *Lancet* **350**, 1670–1673.

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

Hyatt, J. M., Nix, D. E., Stratton, C. W. & Schentag, J. J. 1995 *In vitro* pharmacodynamics of piperacillin, piperacillin–tazobactam and ciprofloxacin alone and in combination against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **39**, 1711–1716.

Lenski, R. E. 1997 The cost of antibiotic resistance from the pespective of a bacterium. *Ciba Found. Symp.* **207**, 131–140.

Lenski, R. E., Simpson, S. C. & Nguyen, T. T. 1994 Genetic analysis of a plamid-encoded, host-genotype specific enhancement of bacterial fitness. *J. Bacteriol.* **176**, 3140–3147.

Levin, B. R., Lipsitch, M., Perot, V., Schrag, S., Antia, R., Simonsen, L., Moore Walker, N. & Stewart, F. M. 1997 The population genetics of antibiotic resistance. *Clin. Infect. Dis.* **24**, S9–S16.

Lipsitch, M. & Levin, B. R. 1997 The population dynamics of antimicrobial therapy. *Antimicrob. Agents Chemother.* **41**, 363–373.

Livermore, D. M. 1992 Interplay of impermiability and chromasomal beta-lactamase activity in imipenem-resistant *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **36**, 2046–2048.

Lloyd, A. L. & May, R. M. 1996 Spatial heterogeneity in epidemic models. *J. Theor. Biol.* **179**, 1–11.

Löwdin, E., Odenholt, I. & Cars, O. 1998 *In vitro* studies of pharmacodynamic properties of vancomycin against *Staphylococcus aureus* and *Staphylococcus epidermis*. *Antimicrob. Agents Chemother.* **42**, 2739–2744.

Massad, E., Lundberg, S. & Yang, H. M. 1993 Modeling and simulating the evolution of resistance against antibiotics. *Int. J. Biomed. Comp.* **33**, 65–81.

Mehtar, S. 1995 Infection control programmes—are they cost-effective? *J. Hosp. Infect.* **30S**, 26–34.

Morris, J. G. Jr, Shay, D. K., Hebden, J. N., McCarter, R. J. Jr, Perdue, B. E., Jarvis, W., Johnson, J. A., Dowling, T. C., Polish, L. B. & Schwalbe, R. S. 1995 Enterococci resistant to multiple antimicrobial agents, including vancomycin, establishment of endemicity in a University Medical Center. *Ann. Intern. Med.* **123**, 250–259.

Nahwani, D. & Wood, M. J. 1993 Penicillins. A current view of their clinical pharmacology and therapeutic use. *Drugs* **45**, 866–894.

Nasell, I. 1997 The quasi-stationary distribution of the closed endemc SIS model. *Adv. Appl. Prob.* **28**, 895–932.

Nissinen, A. (and 9 others) 1995 Development of β-lactamase-mediated resistance to penicillin in middle-ear isolates of *Moraxella catarrhalis* in Finnish children. *Clin. Infect. Dis.* **21**, 1193–1196.

PHLS 1996 Vancomycin-resistant enterococci in hospitals in the United Kingdom—1995. *CDR Weekly* **6**, 1.

PHLS 1997 Epidemic methicillin-resistant *Staphylococcus aureus*. *CDR Weekly* **7**, 191.

Press, W. H., Teukolsky, S. A., Vetterling, W. T. & Flannery, B. P. 1992 *Numerical recipes in Fortran*. Cambridge University Press.

Renshaw, E. 1991 *Modelling biological populations in space and time*. Cambridge University Press.

Rowland, M. & Tozer, T. N. 1995 *Clinical pharmacokinetics, concepts and applications*. Williams & Wilkins.

Salyers, A. A. & Whitt, D. D. 1994 *Bacterial pathogenesis, a molecular approach*. Washington, DC: American Society for Microbiology.

Sanchez, V., Vazquez, J. A., Barth-Jones, D., Dembry, L., Sobel, J. D. & Zervos, M. J. 1992 Epidemiology of nosocomial acquisition of *Candida lusitaniae*. *J. Clin. Microbiol.* **30**, 3005–3008.

Schrag, S. J., Perrot, V. & Levin, B. R. 1997 Adaptation to the fitness costs of antibiotic resistance in *Escherichia coli*. *Proc. R. Soc. Lond.* B **264**, 1287–1291.

Sebille, V., Chevret, S. & Valleron, A. J. 1997 Modelling the spread of resistant nosocomial pathogens in intensive-care units. *Infect. Control Hosp. Epidemiol.* **18**, 84–92.

Seppälä, H., Klaúkk T., Vuopio-Varkila, J., Muotiala, A., Helenius, H., Lager, K. & Huovinen, P. 1997 The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in Group A streptococci in Finland. *New Engl. J. Med.* **337**, 441–446.

Shay, D. K., Goldmann, D. A. & Jarvis, W. R. 1995 Reducing the spread of antimicrobial-resistant organisms. Control of vancomycin-resistant enterococci. *Pediatr. Clin. N. Am.* **42**, 703–716.

Shigesada, N. & Kawasaki, K. 1997 *Biological invasions, theory and practice*. Oxford University Press.

Simmons, B., Bryant, J., Neiman, K., Spencer, L. & Arheart, K. 1990 The role of hand-washing in prevention of endemic intensive-care unit infections. *Infect. Control Hosp. Epidemiol.* **11**, 589–594.

Stilianakis, N. I., Perelson, A. S. & Hayden, F. G. 1998 Emergence of drug resistance during an influenza epidemic, insights from a mathematical model. *J. Infect. Dis.* **177**, 863–873.

Tabaqchali, S. 1997 Vancomycin-resistant *Staphylococcus aureus*, apocalypse now? *Lancet* **350**, 1644–1645.

Tenover, F. C. & McGowan, J. E. Jr 1996 Reasons for the emergence of antibiotic resistance. *Am. J. Med. Sci.* **311**, 9–16.

Wei, X. (and 11 others) 1995 Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* **373**, 117–122.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES