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Epidemiological control of drug resistance and compensatory mutation under resistance testing and second-line therapy

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ABSTRACT

The fitness cost of antibiotic resistance in the absence of treatment raises the possibility that prudent use of drugs may slow or reverse the rise of resistance. Unfortunately, compensatory mutations that lower this cost may lead to entrenched resistance. Here, we develop a mathematical model of resistance evolution and compensatory mutation to determine whether reversion to sensitivity can occur, and how disease control might be facilitated by a second-line therapy. When only a single antibiotic is available, sensitive bacteria reach fixation only under treatment rates so low that hardly any cases are treated. We model a scenario in which drug sensitivity can be accurately tested so that a second-line therapy is administered to resistant cases. Before the rise of resistance to the second drug, disease eradication is possible if resistance testing and second-line treatment are conducted at a high enough rate. However, if double drug resistance arises, the possibility of disease eradication is greatly reduced and compensated resistance prevails in most of the parameter space. The boundary separating eradication from fixation of compensated resistance is strongly influenced by the underlying basic reproductive number of the pathogen and drug efficacy in sensitive cases, but depends less on the resistance cost and compensation. When double resistance is possible, the boundary is affected by the relative strengths of resistance against the two drugs in the double-resistant-compensated strain.

Introduction

The emergence and spread of antimicrobial resistance continues to be a major public health problem (Andersson and Hughes, 2010; Maisnier-Patin and Andersson, 2004). Resistance to all major classes of antimicrobial drugs is increasing (Gandhi et al., 2010; Zhang et al., 2011; Prabaker and Weinstein, 2011; Hughes and Andersson, 2012). For example, the frequency of ciprofloxacin resistance in *Neisseria gonorrhoeae* increased rapidly in the period 1998–2007 (Goldstein et al., 2012). An important step in addressing this problem is to understand the population dynamics of resistance to prevent epidemics of uncontrollable disease in the future (Unemo and Shafer, 2011). This problem has stimulated much research into understanding drug resistance dynamics (Bonhoeffer et al., 1997; Bergstrom and Feldgarden, 2008; Lenski, 1998; Levin et al., 1997; Austin et al., 1997, 1999; Wang and Lipsitch, 2006; Boni and Feldman, 2005). Modelling these dynamics enables the evaluation of alternative schemes for deploying drugs in a population with the aim of optimising those strategies (Bergstrom et al., 2004; Austin et al., 1997; Hansen and Day, 2011).

The observation that resistance comes with a cost in the absence of the drug has raised the possibility of reversion to sensitivity if antibiotics are used prudently. Unfortunately, however, this cost of resistance can be overcome by mutations that reduce the cost (Schrag and Perrot, 1996; Lenski, 1998; Reynolds, 2000; Andersson and Hughes, 2010; Maisnier-Patin and Andersson, 2004). The ultimate success of resistant strains of pathogens with compensatory mutations depends on fitnesses of the strains in both the presence and absence of antibiotics because they evolve in a temporally heterogeneous environment (Schulz zur Wiesch et al., 2010; Tanaka and Valckenborgh, 2011). In the absence of effective strategies for control of resistance it may be only a matter of time before a compensated resistant strain of a pathogen emerges and spreads (Handel et al., 2006).

Despite the growing recognition of compensatory mutation as an important factor in managing drug resistance, little work has been done to understand its impact at the population level. Wijngaarden et al. (2005) considered the dynamics of resistance to a pesticide with the possibility of compensatory mutation.

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Table 1
Variables of the simple model.

Variable	Description
X	Susceptible individuals
U_S	Infections with sensitive strain, untreated
U_R	Infections with resistant strain, untreated
U_C	Infections with compensated resistant strain, untreated
T_S	Infections with sensitive strain, treated
T_R	Infections with resistant strain, treated
T_C	Infections with compensated resistant strain, treated

Resistance reaches fixation when the use of pesticides is high relative to the cost of resistance, which can evolve to be lower. This process is accelerated by recombination. Day and Gandon (2012) also considered the effect of recombination on the evolution of multilocus drug resistance. Handel et al. (2006) studied the emergence of compensatory mutation as an irreversible conversion process. Using a stochastic model that study characterised the probability of emergence of compensated resistant strains of a pathogen and the distribution of the time until emergence.

Given the crucial impact of compensatory mutation on rising frequencies of drug resistance, it will become increasingly important to investigate strategies to combat resistance while still treating cases of disease. In particular, the effective use of second-line drugs may become important. The disease may be controllable by second-line therapies if it is practical to test whether newly detected cases are resistant to the first treatment. Here, we develop an epidemiological model of drug resistance and compensatory mutation in which two alternative treatments are available. The second-line therapy is only used when a new case is tested and found to be resistant to the first drug. We use the model to ask whether any level of treatment would allow sensitive bacteria to prevail; second, we examine what levels of treatment would eradicate disease, under the availability of the second-line drug.

Models of drug resistance evolution

We introduce deterministic models based on an SIS model that is applicable to gonorrhea dynamics (Hethcote and Yorke, 1984), extended to include antimicrobial treatment, evolution of resistance to treatment and compensatory mutation lowering the cost of resistance. We begin with a simple model in which resistance evolves against only the primary therapy. We later relax this assumption in an extended model to allow resistance to both drugs.

The simple model includes three pathogen strains, namely a drug-sensitive strain S, a resistant mutant R carrying a fitness cost of resistance, and a compensated resistant strain C with a mutation that lowers this cost. Susceptible individuals, whose frequency is tracked with X, can be infected with one of the three pathogen strains. All cases receive treatment at the same rate, and both untreated (labelled U) and treated (labelled T) individuals return to the susceptible pool when they recover. Thus our infected population is divided into six disjoint subpopulations according to the strain they are infected by (S, R or C) and whether they are treated (T or U). Table 1 summarises the dynamic variables and Fig. 1 gives a schematic of the process. Infections can convert among classes due to within-host mutation and fixation, as described in detail later.

Modelling transmission and recovery

The transmission parameters are $\beta_S, \beta_R, \beta_C$ respectively for drug sensitive, resistant and compensated (and resistant) strains. Letting β be the baseline transmission of the sensitive strain, we set a cost c of resistance reflected in transmission and compensation $(1-\epsilon)$ of this cost so that the three infection parameters

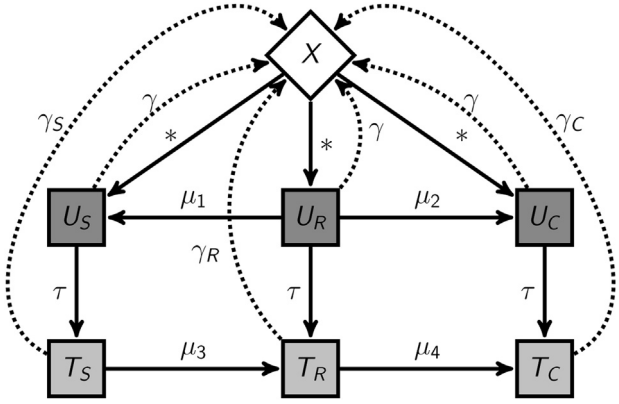

Fig. 1. Model structure for simple model. Variables and rates are as defined in Tables 1 and 2. Here, the asterisks (*) indicate transmission of the sensitive, resistant and compensated strains, whose forces of infection are $\beta_S(U_S+T_S)$, $\beta_R(U_R+T_R)$ and $\beta_C(U_C+T_C)$, respectively.

are given by $\beta_S=\beta$, $\beta_R=\beta(1-c)$ and $\beta_C=\beta(1-c\epsilon)$. The compound parameter $c\epsilon$ is the residual cost of resistance after compensation has occurred. Infected untreated individuals recover at rate γ per individual per unit time. Let τ be the rate per individual at which a case is detected and treated. As an alternative parametrisation we also define $f=\tau/(\tau+\gamma)$ to be the proportion of cases treated.

To parametrise recovery under treatment, first consider the case in which a single class of antibiotic is available. The duration of infection with the sensitive strain is reduced by σ under treatment. Resistance increases the duration of treated infection through parameter b while infection with the compensated resistant strain lengthens the duration through parameter k. Specifically, if only a single treatment is available, the recovery rates for treated classes are $\gamma/(1-\sigma)$, $\gamma/(1-\sigma(1-b))$ and $\gamma/(1-\sigma(1-k))$ respectively for S, R and C. We now generalise these recovery rates for when there is an alternative, second-line treatment. We model a situation in which each new detected case is tested for resistance to the first drug, and if resistance is found, the second-line therapy is used. We assume for simplicity that this second-line therapy is always effective and resistance does not evolve to it. Let ρ be the proportion of detected cases that are tested for drug resistance. The recovery rates for treated cases are then

$$\gamma_S = \frac{\gamma}{1-\sigma}$$
$$\gamma_R = (1-\rho)\frac{\gamma}{1-\sigma(1-b)} + \rho\frac{\gamma}{1-\sigma}$$
$$\gamma_C = (1-\rho)\frac{\gamma}{1-\sigma(1-k)} \quad + \rho\frac{\gamma}{1-\sigma}.$$

Conversion among resistance states

The conversion rates between strains depend on both mutation and within-host fixation, which in turn depend on selective pressures. Let ν be proportional to the mutation rate per individual per gene per unit time. The probability of fixation is approximately twice the selective coefficient (Haldane, 1927); we therefore allow ν to subsume the factor of 2 and derive the selective coefficients in each of the four within-host conversion processes shown in Fig. 1.

To determine how μ_1 relates to the fitness parameters, first note that in the absence of the drug the fitness values of sensitive relative to resistant strains are in the ratio $(1:1-c)$. In a within-host