Simulating the spread of resistance to antibiotics

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Antibiotic resistance is a major clinical and public health issue causing difficulties in treating infectious diseases and increased risk for complications that lead to fatal outcome. The epidemiology of resistance is a function of the innate characteristics of the bacteria, transmission rates and the consumption of antibiotics. While there are cases where prudent usage of antibiotics leads to decrease in resistant frequency, there are examples where reduction does not lead to reversibility. The dynamics of this complex relationship can be profitably explored by system dynamics simulations. In this paper a generic model describing the transmission of commensal bacteria within a community exposed to different levels of antibiotics is simulated and analytical expressions describing the conditions for reversibility are derived. It is shown that cutting back the volume of antibiotics is necessary but not sufficient to reduce resistance frequency. The biological cost for sustaining resistant traits (fitness cost) and the lateral transmission of genetic material play a critical role.

Keywords: Antimicrobial resistance, modeling, fitness cost

Introduction

Low but detectable number of bacteria carrying resistant genes existed before industrial manufacturing and use of antibiotics; this is not too surprising giving that penicillin for example is produced by microorganisms (Levy 2002). The extensive use of antibiotics however generated wide spread genetic changes within the bacteria making them capable of surviving in a toxic environment. At present the frequency of resistant strains is high and reaches more than 25% in several EU member states resulting in the death of thousands of patients and enormous healthcare costs every year (ECDC/EMEA 2009).

The usage of antibiotics triggers the evolution of drug resistance through a selective pressure, on a micro-ecological scale, favoring bacteria carrying genetic determinants capable of expressing resistance. Subsequently sensitive bacteria accept resistant genes via transmission of plasmids[1] and other genetic materials (Levy 2002, Alanis 2005, Andersson 2005). These genetic alterations equip resistant bacteria with biological mechanisms by which resistance to antibiotics is achieved in one or more of the following ways: 1-target molecules are altered to prevent antibiotic binding, 2- preventing the drug from entering the cell 3- degradation of the antimicrobial agent and 4- pumping the agent out (Levy 2002, Alanis 2005, Andersson 2005).

The reversibility of resistance

There are a number of documented cases, mainly in hospitals, where decline in resistance has been observed following reduction in the use of antibiotics. However resistant frequency does not return to previous value and the reverse reaction is very slow (Barbosa and Levy 2000). A recent study concludes that a major reduction in the use of antibiotics in a Swedish community over a period of 24 months did not result in a corresponding decline in resistance (Sundqvist 2010).

One would expect that in order for reversibility to occur resistance should impair a biological disadvantage in the absence of antibiotics. Indeed many studies have shown that most resistance mechanisms engender a reduction in bacterial fitness (Andersson and Levin 1999, Björkman and Andersson 2000, Lenski 1997). The fitness cost, which is believed to be a consequence of diverting energy from reproduction to upholding resistance, is measured by the relative rates at which sensitive and resistant bacteria 1- grow and die inside and outside hosts, 2- are passed on between hosts or 3- are cleared from infected hosts. Although fitness cost effects are observed there is however a qualification. Many of these studies have been done in laboratory using antibiotic resistant genes with no evolutionary history while bacteria can in fact reduce the burden associated with resistance through compensatory evolution (Andersson and Levin 1999, Björkman and Andersson 2000, Lenski 1997).

Modeling antibiotic resistance

Various mathematical models have been developed to describe how various factors contribute to the spread of drug resistance and interpret empirical data for community and hospital acquired infections (Austin et al. 1997, Austin et al. 1999a, Austin et al. 1999b, Homer et al. 2000, Levin 2002, Lipsitch 2000, Massad et al. 1993, Pelupessy et al. 2002, Webb et al. 2005). Homer et al. and Webb et al. make use of bacterial population dynamics while in the other models human population dynamics is employed.

The purpose of this work is to describe the evolution and prevalence of resistance in a human community making use of a deterministic epidemiological model developed by (Austin et al. 1997). The equilibrium states and conditions of reversibility are described in terms of the relative fitness of resistant bacteria, antibiotic consumption and transmission rate between hosts.

The model

Commensal flora exists within its human hosts asymptomatically, but may turn pathogenic if the microbes enter sterile sites of the body and multiply. In the model below, it is assumed initially that a fraction of the population is infected by a commensal bacterium sensitive to antibiotics but capable of mutation to a resistant strain. Antibiotic is administered separately

from the colonization condition due to infection with another pathogenic or prophylactically. Hosts therefore are present in five states, 1- susceptible not taking antibiotics (X), 2- susceptible taking antibiotics (X_a), 3- infective sensitive (Y), 4- resistant not taking antibiotics (Z) and 5- resistant taking antibiotics (Z_a).

It is assumed further that the community consists of a constant number of individuals N, and new susceptible hosts enter the population at a rate $\lambda = \mu N$ where $1/\mu$ is the average duration time. Following the SIR tradition (Sterman 2000) uninfected individuals are converted into infected at a rate equal to the product of their numbers and a transmission constant designated by β or β' in the equations below (law of mass action). Colonized individuals become free form infection after a clearance time $1/f_s$ or $1/f_r$ depending on whether the bacteria are sensitive or resistant. Antibiotics are administered at a fractional rate[2] γ. Treatment is continued for a period of time 1/g. Under the selective pressure of antibiotics a small fraction of the population σ that is sensitively colonized will select pre-existing resistant mutants. The emerged resistant population passes on resistant genes to sensitive hosts through horizontal plasmid transmission with a transmission coefficient ξ. With these assumptions the dynamics of the system is described by the following set of differential equations

$$\frac{dX}{dt} = gX_a + f_sY + f_rZ + \mu N - \beta'X(Z + Z_a) - \beta XY - (\gamma + \mu)X \quad (1)$$

$$\frac{dX_a}{dt} = f_rZ_a + (1-\sigma)\gamma Y + \gamma X - \beta'X_a(Z + Z_a) - (g + \mu)X_a \quad (2)$$

$$\frac{dY}{dt} = \beta XY - f_sY - (1-\sigma)\gamma Y - \sigma\gamma Y - \mu Y - \xi Y(Z + Z_a) \quad (3)$$

$$\frac{dZ}{dt} = \beta'X(Z + Z_a) + \xi Y(Z + Z_a) + gZ_a - (f_r + \gamma + \mu)Z \quad (4)$$

$$\frac{dZ_a}{dt} = \beta'X_a(Z + Z_a) + \gamma Z + \sigma\gamma Y - (f_r + g + \mu)Z_a \quad (5)$$

and

$$N = X + Y + Z + X_a + Z_a$$

The skeleton of the system structure is shown in Figure 1, auxiliaries and arrows are omitted for the sake of clarity. Moreover with this representation the flows in to and out from the stocks are explicitly shown

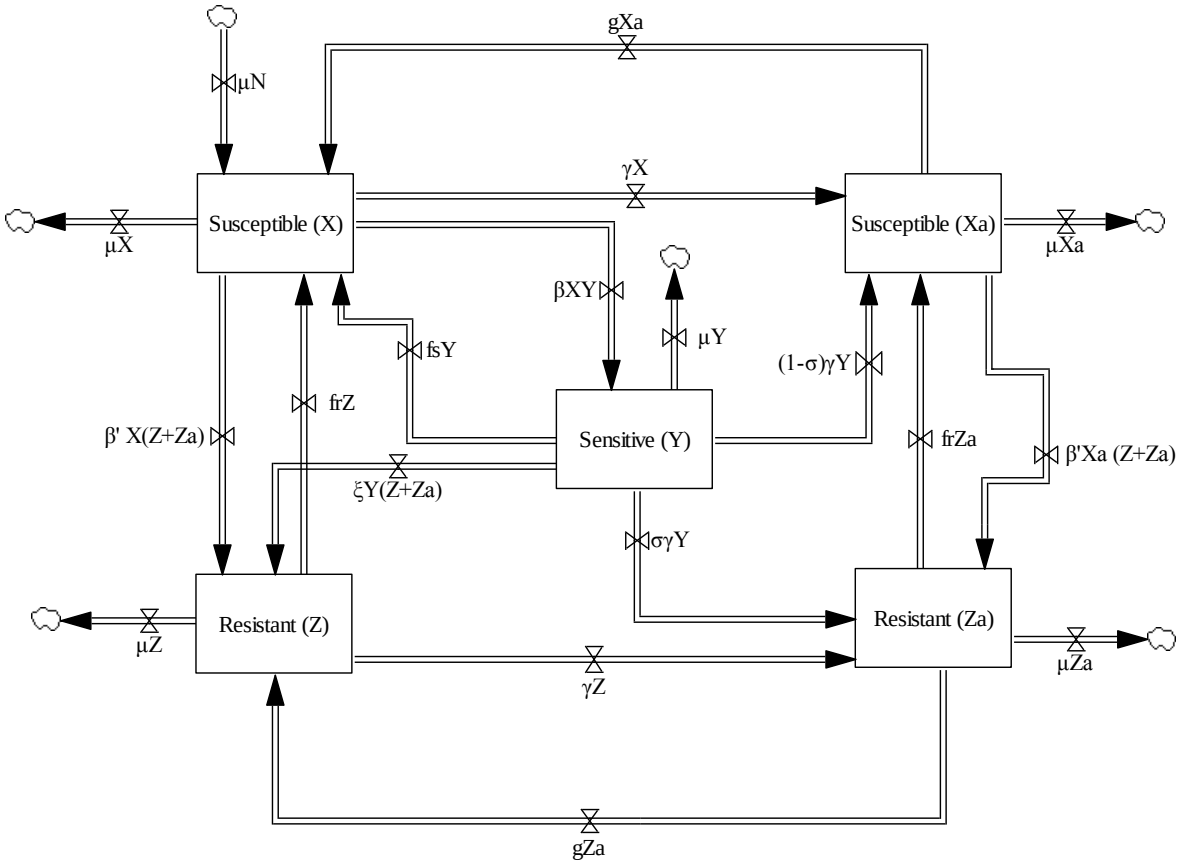

Figure 1. System structure, arrows and auxiliaries not shown

Parameters of the model

The size of the population N is set to 10000 individuals distributed initially between susceptible (X (0) = 9900) and sensitive (Y(0) = 100). Antibiotic consumption begins abruptly at month 10 and is maintained at constant fractional rate for a period of 180 months. Clearance time $1/f_s$, treatment time 1/g and average duration time $1/\mu$ are assigned the values 1 month, 0.33 months and 72 months respectively as in (Austin et al. 1999a). Clearance time from resistant bacteria $1/f_r$ is varied within a broad range in order to explore the prevalence of resistance and the conditions of reversibility. The ratio f_r/f_s is taken as a measure of the fitness cost.

Under the assumption of random encounters the transmission coefficient β can be equated to cp/N where c is the contact frequency (1/month) and p the probability of infection after an encounter. p is assigned a value of 0.01 while c will be varied between 200 and 300 encounters per month. Since carriers of resistant strains are not quarantined or treated in a special way no distinction is made between β and β'

The plasmid transfer coefficient ξ is analogous to but most likely less than β (Austin et al. 1997). The rationale is that it is more laborious to convey plasmids to sensitive bacteria in comparison to transmission between sensitively colonized and susceptible hosts. In all the simulations ξ is assigned a value of 0.6β. As mentioned previously treatment with antibiotics selects for a fraction $\sigma<<1$ carrying resistant traits, the value of σ in all runs is 10^{-4} and with a treatment rate $\gamma = 0.1$/month the mutation fraction rate per month $\gamma\sigma$ is comparable to the values reported by (Homer et al. 2000).

Simulation and analysis

a) Conditions at equilibrium and reversibility

Simulation results predicting resistant frequency at different values of β and f_r are shown in Figures 2 – 4. Figure 5, shows the variability of sensitive population for the case β = 0.00025. Use of antibiotics starts at month 10 and take the shape of 180 month long pulse. Tables 1 – 3 display the ratio f_r/f_s. Fitness cost increases with f_r/f_s and is zero when $f_r = f_s$. The other entries in the tables are explained below.

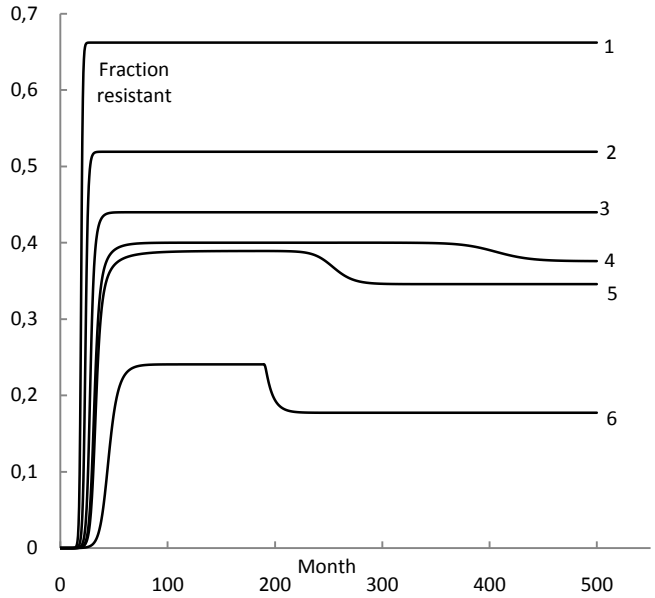

Figure 2. Fraction resistant vs. time, β = 0.0003, γ = 0.1 f_s = 1, f_r variable

Run	f_r/f_s	$1/R_o''$	$1\text{-}1/R_o$	$1\text{-}1/R_o'$
1	1.00	0	0.662	0.662
2	1.43	0.238	0.519	0.662
3	1.67	0.370	0.440	0.662
4	1.79	0.437	0.400	0.662
5	1.82	0.454	0.389	0.662
6	2.00	0.556	0.329	0.662

Table 1. Parameters affecting reversibility, β = 0.0003

As can be seen from these diagrams resistant frequency may rise quickly and remain at high levels. Also the fraction of sensitive population may well decline to zero. Equilibrium values and the possibility of reversibility after termination of antibiotics can be found from equations (1) to (5). Since there is no antibiotic consumption $X_a = Z_a = 0$ and for the case $Y \rightarrow 0$ there are only two populated states namely X and Z. At steady state the time derivatives are zero hence

$$\frac{X}{N} = \frac{f_r + \mu}{N\beta} = \frac{1}{R_o} \qquad (6)$$

$$\frac{Z}{N} = 1 - \frac{1}{R_o} \qquad (7)$$

These relations are the same as for a two states epidemic system, R_o being the basic reproductive ratio[3] (Anderson and May 1991).

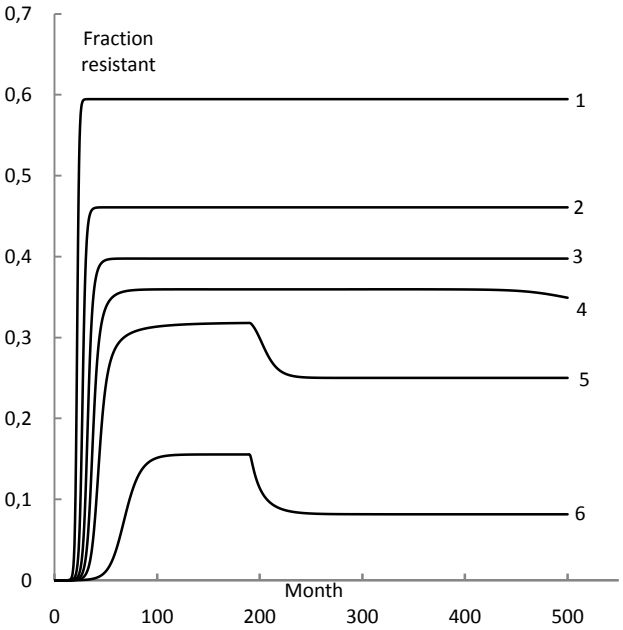

Figure 3. Fraction resistant vs. time, β = 0.00025, γ = 0.1 f_s = 1, f_r variable

Run	f_r/f_s	$1/R_o''$	1-1/R_o	1-1/R_o'
1	1.00	0	0.594	0.594
2	1.33	0.222	0.461	0.594
3	1.49	0.328	0.397	0.594
4	1.59	0.392	0.360	0.594
5	1.67	0.444	0.328	0.594
6	1.82	0.545	0.267	0.594

Table 2. Parameters affecting reversibility β = 0.00025

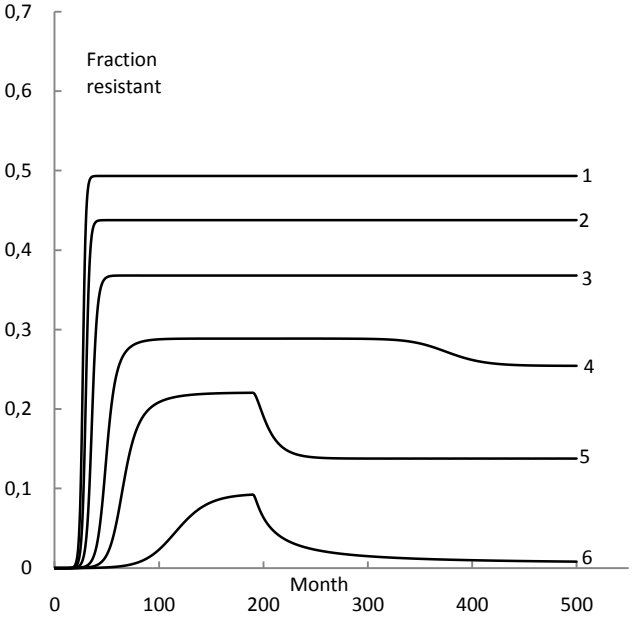

Figure 4. Fraction resistant vs. time, β = 0.0002, γ = 0.1 f_s = 1, f_r variable

Run	f_r/f_s	$1/R_o''$	1-1/R_o	1-1/R_o'
1	1.00	0	0.493	0.493
2	1.11	0.093	0.438	0.493
3	1.25	0.208	0.368	0.493
4	1.41	0.340	0.289	0.493
5	1.49	0.410	0.247	0.493
6	1.59	0.489	0.199	0.493

Table 3. Parameters affecting reversibility β = 0.0002

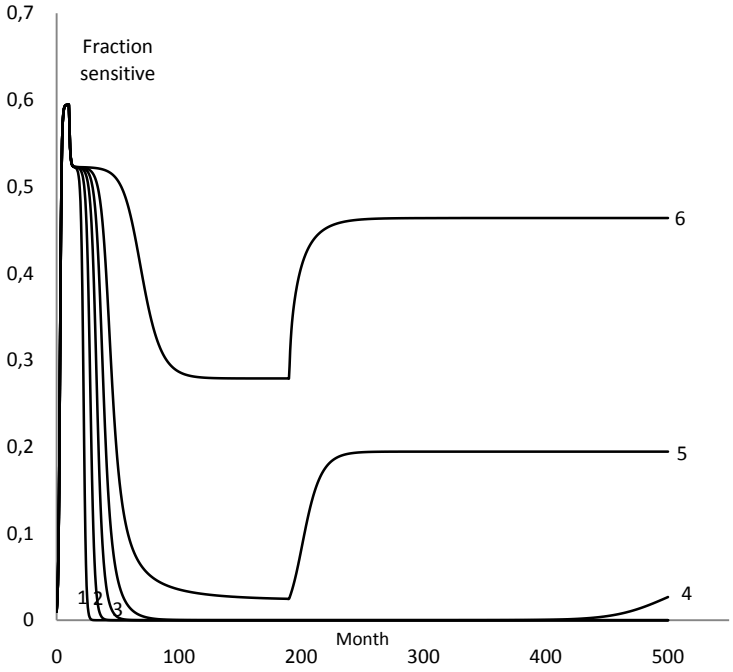

Figure 5. Fraction sensitive hosts vs. time, β = 0.00025
γ = 0.1, numbers on curves have same significance as Fig. 3

When Y > 0 Equations (1), (3) and (4) give

$$\frac{X}{N} = 1 - \frac{f_r - f_s}{N\xi} \tag{8}$$

$$\frac{Y}{N} = \frac{1}{N\xi}(-\beta X + f_r + \mu) \tag{9}$$

$$\frac{Z}{N} = \frac{1}{N\xi}[\beta X - (f_s + \mu)] \tag{10}$$

Run	X/N (sim)	X/N (cal)	Y/N (sim)	Y/N (cal)	Z/N (sim)	Z/N (cal)
1	0.40	0.41	0	0	0.59	0.59
2	0.54	0.54	0	0	0.46	0.46
3	0.60	0.60	0	0	0.40	0.40
4	0.62	0.61	0.03	0.05	0.35	0.34
5	0.56	0.56	0.19	0.19	0.25	0.25
6	0.45	0.45	0.46	0.46	0.08	0.08

Table 4. Comparison between calculated and simulated values at equilibrium β = 0.00025

Estimates from (8) - (10) compare favorably with simulation results as is seen in Table 4. Equations (8) to (10) can also be applied to formulate the conditions of reversibility. As is seen from Figures 3 and 5 reduction in resistant frequency occurs when Y/N > 0. From (8) and (9) we then get

$$\frac{f_r - f_s}{N\xi} > 1 - \frac{f_r + \mu}{N\beta} \tag{11}$$

The right hand side is the same as (7), putting $R_o'' = N\xi/(f_r - f_s)$ we have

$$\frac{1}{R_o''} > 1 - \frac{1}{R_o} \tag{12}$$

The condition for more or less complete reversibility requires that Z/N → 0, then from (8) and (10) we have

$$\frac{f_r - f_s}{N\xi} \approx 1 - \frac{f_s + \mu}{N\beta} \tag{13}$$

and naming $N\beta/(f_s + \mu)$ by R_o' we get

$$\frac{1}{R_o''} \approx 1 - \frac{1}{R_o'} \tag{14}$$

Comparing the curves in Figures 2 – 4 with the entries in adjacent tables we see that Equations (12) and (14) correctly predict the onset of decline in resistant frequency.

b) Effect of antibiotics rate

Figures 6 and 7 illustrate the effect of antibiotic consumption at two levels of f_r/f_s.

In these simulations γ is either 0, reduced by a factor of 100 or increased 20 times in comparison to earlier runs. When γ = 0 there is initially one host in the system carrying resistant bacteria ($Z(0) = 1$).

The equilibrium level reached in Figure 6 is identical to that of curve 3 Figure 3, but the slope depends on prescribing rate. On the other hand Figure 7 shows two final states; the lowest matches the level that resistant frequency drops to after cessation of antibiotics while the other level is the maximum resistant frequency attainable namely $1 - 1/R_o$ as Eq. (7).

It has been suggested that a threshold level of antibiotic usage is needed to establish resistance at a significant level (Austin et al. 1997, Homer et al. 2000). The results above show no such occurrence. In fact as is shown in Figures 6 and 7, it is possible for resistance to develop to an epidemic state even without consumption of antibiotics if a single resistant carrier enters the system. To look further into this issue simulations at a higher f_r/f_s ratio are performed. The results are shown in Figure 8. Observable resistant frequency now appears when γ exceeds 0.2/month. Also at this level of fitness cost conditions for reversibility are fulfilled since with f_r/f_s = 2.00, $1/R_o''$= 0.666 which is larger than 1- 1/ R_o' (see table 2 above). However no reversal takes place at very high antibiotic consumption rate due to eliminating all sensitive bacteria.

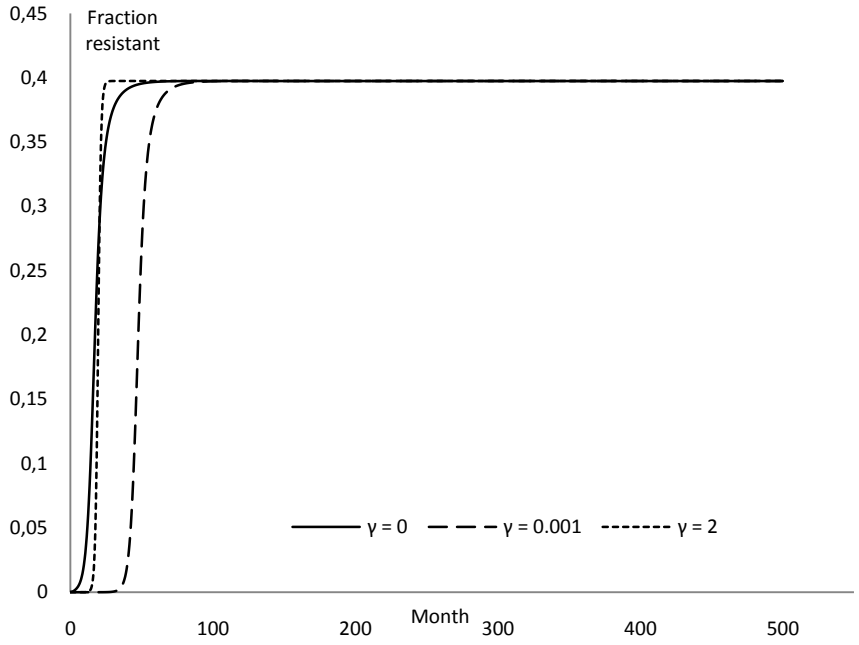

Figure 6. Dynamics of resistance development at different antibiotics rate γ, β = 0.00025, f_r/f_s = 1.49 as curve 3 Fig. 3

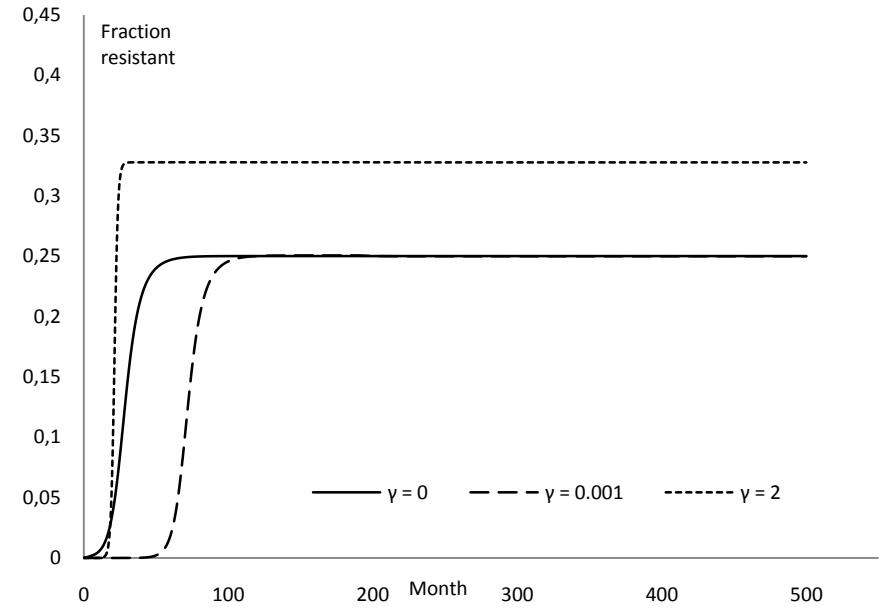

Figure 7. Dynamics of resistance development at different antibiotics rate γ, β = 0.00025, f_r/f_s = 1.67 as curve 5 Fig. 3

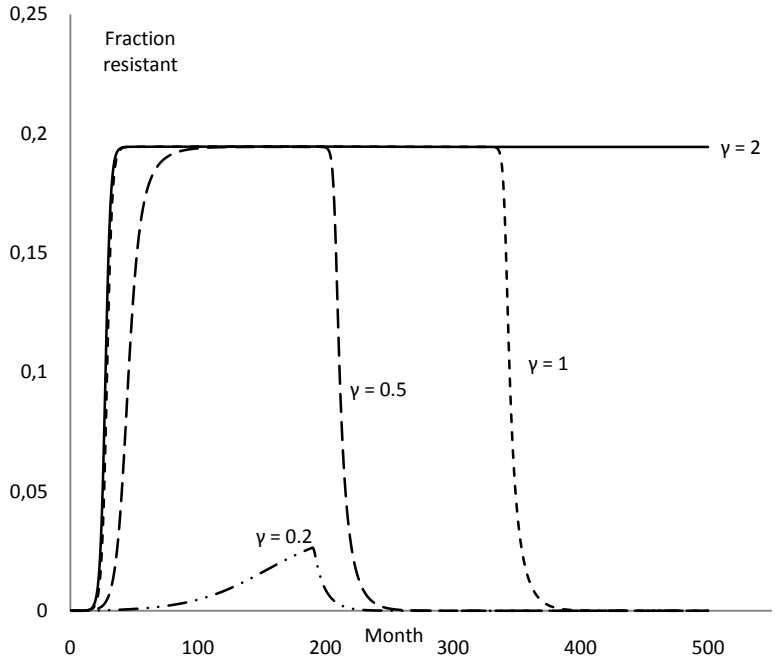

Figure 8. Presence of threshold, $\beta = 0.00025$, $f_r/f_s = 2.00$

Exogenous inflow of resistance carriers

The analysis so far considered the inflow from the environment to consist only of susceptibles. If carriers of resistant bacteria also enter the system from the outside, then the prevalence of resistance will be more problematic. This is illustrated in Figure 9 where the magnitude of the extra flow is equivalent to 5% of the influx of susceptible hosts. Comparing Figures 4 and 9 it is interesting to notice that the effect is not constant but is rather stronger at low resistant levels.

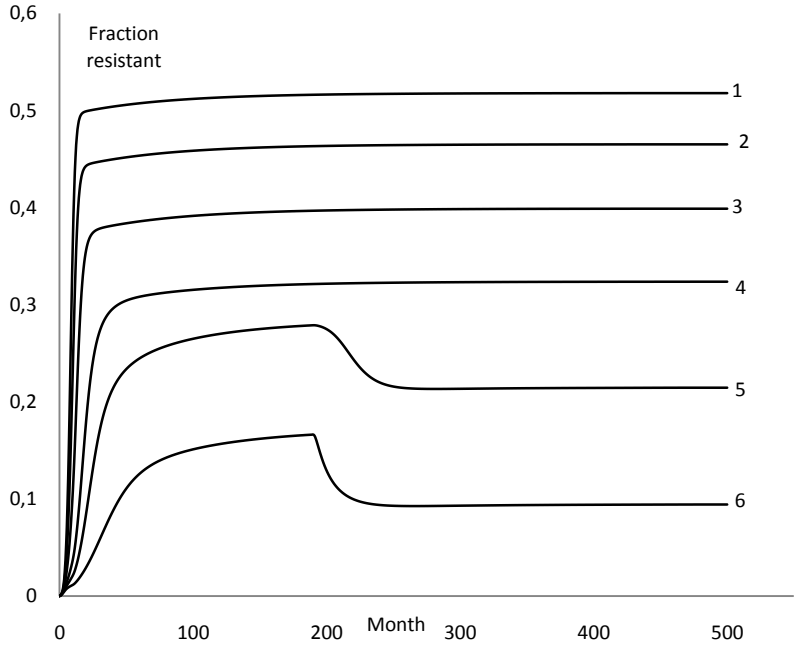

Figure 9. Fraction resistant vs. time, same parameters as Fig.4 but with an additional exogenous flow of resistance carriers

Summery
System dynamics simulation is used to explore the spread of resistant bacteria in a community. Initially there are no resistance carriers in the system. The introduction of antibiotics however triggers their emergence. Subsequently the dynamics is controlled by the transmission of resistant mutants to sensitive bacteria and direct transmission between hosts. The levels at steady state and conditions for reversibility are expressed in terms of dimensionless ratios as is traditionally done in epidemiology. The model predicts that if resistance does not entail a biological disadvantage than reversibility will not materialize at low consumption levels of antibiotics. An equally depressing finding is that without sufficient fitness cost migration into the community by few resistance carriers will initiate the spread of resistant genes even though no antibiotic is administered. This suggests that understanding the mechanism behind resistance cost and how bacteria can compensate for it, is an important element in designing new antimicrobial drugs.

Notes

1. Plasmids are small ring shaped self replicating DNA molecules present in bacteria. They carry extra traits such as resistant genes not specified by the cell's chromosome. Plasmids transfer resistant traits through a number of mechanisms. See (Levy 2002) for an interesting historical background
2. Fractional antibiotic rate γ is the fraction of the community using antibiotics per unit time. Multiplying γ with the duration of treatment gives the proportion of individuals undergoing treatment. The value of γ used in most of the runs was 0.1/month, with treatment duration of 0.3 month this is equivalent to 3% of the population.
3. For a compartmental model as this one the basic reproductive ratio R_o is the average number of secondary infections produced when a single infected host is introduced into a population which is entirely susceptible. An epidemic is expected to spread when $R_o > 1$. Methods for calculating R_o for various epidemiological systems is described by (Heffernan et al. 2005)

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