

Do we really have to take all our medicine?  
Predicting the consequences of large-scale antibiotic misuse.

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**Abstract**

Failure to properly complete antibiotic treatment can result in the eventual development of bacterial strains resistant to antibiotic therapy. If present trends in antibiotic misuse continue, infections that are easily treated today may not be so in the future. We consider a stochastic model and examine the conditions of misuse under which resistant strains will thrive. Virulence differences in the competing strains are taken into consideration as a possibility for superinfection. The probability of extinction is calculated for each strain. We predict the long-term effects of antibiotic misuse and consider the specific case of *Streptococcus pneumoniae*, the bacteria that causes pneumonia.

# 1 Introduction

The rise of bacterial strains resistant to antibiotic therapy is a new problem with old roots. Since the 1940's, widespread availability of antibiotics has been a part of American life. "Miracle drugs" like penicillin transformed the medical world by turning once lethal illnesses into easily treatable infections [17]. However, until very recently, the clinicians that routinely prescribed these medications and the public that willingly consumed them were blissfully unaware that as the human race waged war on bacteria, bacteria were fighting back. Now, nearly half a century after the dawn of antibiotic salvation, humanity takes notice as our treatments begin to falter.

The lifespan of a human being exceeds that of a bacteria by orders of magnitude. As a result, a case of pneumonia that lasts two weeks in a human might represent thousands of generations of bacterial progeny. With each generation, some species evolution inevitably occurs. Treating the bacteria with antibiotics causes them to undergo selective evolution [5]. Those cells less vulnerable to the methods by which the drug attacks will outlive those that are not. As the weaker bacteria die and the bacterial community diminishes in size, the pain of the infection may subside, and the infected individual may choose to stop treatment. If this occurs before all the bacteria are eliminated, the remaining bacterial cells and their more resistant traits will be able to freely proliferate, thus increasing the reservoir of resistant genes in the population of the pathogen.

If we view this example of evolutionary pressure in the context of all cases of pneumonia treated with antibiotic therapy in the last sixty years, the magnitude of the problem of selective evolution becomes clear. We are perhaps justified in suspecting that misuse of antibiotics is a non-trivial factor in the development of resistant strains.

Since the advent of antimicrobial therapy, enthusiastic pharmaceutical companies have devoted many resources to the discovery, production, and improvement of antibiotics. However, as bacterial strains continue to evolve more sophisticated methods of resistance, the challenge of defeating them increases [10]. It has been estimated that 30% of bacterial strains are resistant to antibiotics [17]. Today, the World Health Organization reports that new drugs are no longer being produced fast enough to replace those that have lost effectiveness [18]. This is sobering news in light of the many factors currently contributing to the rise of new antibiotic resistant bacteria. The countless number of people who neglect to complete their entire course of antibiotic treatment, are not the only ones at fault. Physicians also share the blame. The Center for Disease Control estimates that twenty percent of all antibiotic prescriptions written each year are for viral infections which do not respond to antibiotics

[13]. Alarming, in one survey 80% of physicians questioned confessed to having prescribed antibiotics as a result of patient pressure and against their better judgment [17]. Approximately 50 million unnecessary prescriptions are prescribed annually. Industry also contributes to this epidemic of misuse. Only half of the antibiotics used each year are prescribed to humans. Many of the same medications prescribed for human treatment are distributed to animals. The animals are exposed to low dosages for long periods of time. The drugs are used for treating or preventing infection and to promote growth. These low dosages encourage growth of resistant bacteria. Antibiotics are used to control or prevent infections in agriculture. Growth of resistant strains is possible in the areas where the aerosol antibiotics become dilute, thus removing only the sensitive, non-resistant bacteria. The resistant strain can then be introduced to the intestinal tract of humans after consumption of the produce [17]. While it is interesting to consider the degree to which each of these factors contributes to the increasing trend in antibiotic resistance, we choose to focus only on the role of patient negligence.

It is our goal to examine analytically the effects of failure to complete medication, herein referred to as antibiotic misuse, on the development of antibiotic resistant strains. To do this we specifically consider the evolution of penicillin resistance in *Streptococcus pneumoniae* because it is a phenomenon already well observed in the medical community. At present, estimates of *S. pneumoniae* strains that have developed penicillin resistance range from three to thirty-five percent [14]. However, penicillin is simply one of many antibiotics found to be insufficient in treatment. Strains of *S. pneumoniae* have become resistant to numerous antibiotics including penicillin, erythromycin, macrolides, tetracycline, TMP/SMX, and Chloramphenicol [3]. This pathogen causes the pneumococcal diseases otitis media (ear infection), sinusitis, arthritis, perionitis, sepsis/bacteremia, meningitis, pneumonia, neurological sequelae and/or learning disabilities after meningitis, and deafness after recurring otitis media [13], [14]. These infections cause approximately 100,000-135,000 hospitalizations and 40,000 deaths annually in the United States [13]. Pneumonia caused by *Streptococcus pneumoniae* has become the fifth leading cause of overall deaths and is the highest cause of deaths due to infection [16]. Once an antibiotic resistant strain emerges, it may easily spread far and wide. Investigators have noted the migration of resistant strains for example, from Spain to the U.K, the U.S, South Africa, and several other countries [14]. The movement of the resistant strains creates the potential for a world-wide epidemic of untreatable pneumonia. Hence, the spread of these untreatable strains is not trivial.

To determine the role of antibiotic misuse in preventing or inducing a potentially uncontrollable *S. pneumoniae* epidemic, we develop a generalized stochastic S-I-S

model is developed in which individuals who fail to complete antibiotic treatment may develop an infection of resistant bacteria. By varying the probability that an individual fails to complete treatment we expect to account for the contribution of antibiotic misuse to the development of a resistant strain. We investigate the possibility that a resistant strain eventually replaces the treatable strain as a result of misuse by calculating the probability of extinction of each strain.

In Section 2 we propose a model for this phenomenon. In Section 3 we use continuous-time Markov chain analysis to calculate the probability of extinction for each of the two strains. In Section 4 we examine the effects of some parameters on the probability of extinction for each strain. In Section 5, we simulate the development of a resistant strain and its interactions with the non-resistant strain for varying parameter values. In section 6, we discuss the biological implications of our findings and suggest future avenues of investigation.

## 2 The Model

We consider a modified, two-strain, S-I-S stochastic model with superinfection to examine the development of a resistant bacterial strain (see Figure 1). The population of uninfected, susceptible individuals is represented by state  $S$ . States  $I_1$  and  $I_2$  represent individuals infected with non-resistant and resistant bacteria, respectively. States  $T_1$  and  $T_2$  consist of infected populations undergoing antibiotic treatment. We use  $N = S + I_1 + T_1 + I_2 + T_2$  to represent the total population. Individuals in  $I_i$  states are assumed to be infectious. Those in  $T_i$  states are not.

Individuals infected with non-resistant bacteria will remain in an infectious state,  $I_1$ , until symptoms appear and antibiotic therapy begins, at which point they move to state  $T_1$ . The possibility of superinfection is also considered: individuals infected with non-resistant bacteria may move to state  $I_2$  via contact with that population.

When in state  $T_1$  individuals who complete treatment will return to the susceptible state,  $S$ . Those who do not will progress to one of three alternatives. They may (i) return to state  $S$  when the immune system eliminates remaining bacteria, (ii) return to state  $I_1$  due to a resurgence of original bacteria, or (iii) advance to state  $I_2$  if residual bacteria have evolved antibiotic resistance due to the selective pressure of antibiotic therapy.

Individuals who enter state  $I_2$ , either by failing to complete treatment in  $T_1$  or by direct contact with others in  $I_2$ , will remain in that state until symptoms appear and treatment begins, at which point they move to state  $T_2$ . In  $T_2$ , individuals are treated with the same antibiotic administered to those in state  $T_1$  but due to the nature of

$I_2$  infectives, this treatment will be highly ineffective in eliminating the resistant bacteria, and even individuals who complete treatment in state  $T_2$  will return to the susceptible state at a very low rate. Those who fail to complete treatment will remain in state  $T_2$ .

We recognize that our model is very simple and does not include all the factors that contribute to the development of resistant strains. For instance, we do not include the possibility that individuals in  $T_2$  might be treated with an alternate prescription to which the bacteria is not resistant. Consequently we neglect the possibilities that multiple resistant strains might develop simultaneously or that individuals might not have to spend such an extended period of time in the treatment state for strain 2. In addition, factors such as bacterial mutation and adaptation independent of antibiotic misuse are not specifically considered. Nonetheless, we feel that this simple model reflects some of the more important aspects of antibiotic misuse and will allow us to study the dynamics of disease.

Table 1: Parameter List

Parameters	Description
$\beta_i$	per capita contact rate of individuals in $I_i$
$\alpha$	per capita birth rate
$\mu$	natural mortality rate
$v_i$	disease induced mortality rate for strain $i$ (dependent on virulence of strain $i$ )
$\phi_i$	rate at which infected individuals seek treatment, here considered to be the same as the rate at which first symptoms appear
$\gamma_a$	recovery rate of individuals infected with strain 1 who complete treatment
$\gamma_b$	recovery rate of individuals infected with strain 1 who do not complete treatment
$\gamma_2$	recovery rate of individuals infected with strain 2 who complete treatment
$p_i$	probability that an individual infected with strain $i$ completes antibiotic treatment
$q_1$	probability that an individual infected with strain 1 will remain infected if treatment is not completed
$q_2$	probability that an individual infected with strain 1 will become infected with strain 2 as a result of failure to complete treatment

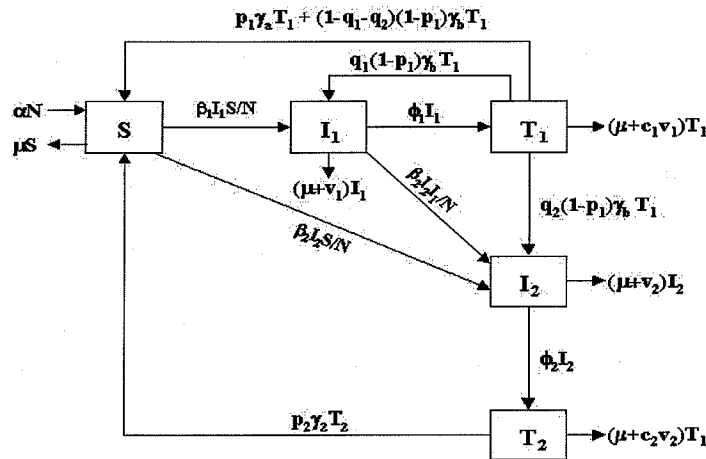


Figure 1: A model for the development of antibiotic resistant bacteria as a result of antibiotic misuse. Since this is a stochastic model, all rates are assumed to be parameters of exponential distributions.

### 3 Methodology

The goal of our research is to examine conditions under which the two strains coexist and under which the resistant strain replaces the non-resistant strain. To do this we first calculate the probability of extinction of each strain in terms of the parameters that will influence its extinction. This is done by finding the inverse of each strain's basic reproductive number,  $R_0$  [4]. The basic reproductive number represents the expected number of secondary infections caused by a single infectious individual in a population of susceptible, a useful tool in predicting the future of epidemic diseases. In general, if  $R_0 > 1$ , the disease goes extinct with probability  $\frac{1}{R_0}$  whereas it dies out with probability 1 when  $R_0 \leq 1$ .

As a result of the two-way interaction between states  $I_1$  and  $T_1$  in our model, conventional methods for calculating  $R_0$  become complicated and alter its interpretation

as a probability of extinction. Hence, we use the method of continuous-time Markov chain analysis outlined by Hernández [4]. This method involves creating an absorbing state model (Figure 2) and using a matrix of transition probabilities to calculate  $R_0$  for each strain (Figures 1 and 2). We use  $R_0^{[1]}$  and  $R_0^{[2]}$  to represent the number of secondary infections caused by an individual when infected with strain 1 and strain 2 respectively.

### 3.1 Absorbing State Model

To begin the absorbing state model, we separate the states  $S$ ,  $I_1$ ,  $T_1$ ,  $I_2$ , and  $T_2$  into three categories: active infectious states, passive infectious states, and absorbing states. An infected individual in an active infectious state infects others. In a passive infectious state the individual is infected but not infectious, yet still communicates with an active infectious state. Absorbing states mark the end of the infectious period; once entered, these states are never left [11]. We direct all possible ways of ending an infectious cycle into one absorbing state,  $\Delta$ . In our model,  $I_1$  and  $I_2$  are actively infectious populations. Since we assume that the individuals in the  $T_i$  states are infected but not infectious,  $T_1$  is passively infectious since it communicates with  $I_2$ , but  $T_2$  does not communicate with an active infectious state. So,  $T_2$  along with  $S$  and the deaths from each state make up the absorbing state. Hence the active infectious states are  $I_1$  and  $I_2$ , the passive infectious state is  $T_1$ , and  $\Delta$  consists of  $S$ ,  $T_2$ , and deaths. Figure 2 illustrates a modified transition model which we use to find the expected time an individual spends in each state before going to absorption.

### 3.2 Transition Matrix

We now construct a matrix  $P$  of one-step transition probabilities where each element  $p_{ij}$  represents the probability that an individual moves directly from state  $i$  to state  $j$ . Finding  $\lim_{n \rightarrow \infty} P^n$  yields a matrix with identical rows. The elements in each column are the same, indicating that as time goes to infinity the number of visits an individual makes to each state becomes independent of their state of origin. So we only concern ourselves with a single row of the matrix which we call the vector  $\Pi$ . From this we compute the expected time spent in state  $j$  and multiply it by  $\beta_j$  which illustrates the general process for calculating  $R_0$  when dealing with one infected state.

In our model, we specifically look at two strains of bacteria causing disease and deal with two infected states. We need to calculate  $R_0^{[1]}$  for strain 1 and  $R_0^{[2]}$  for strain 2, which complicates the calculation of a general  $R_0$ . To do this, we must use two transition matrices,  $P_{I_1}$  and  $P_{I_2}$ , and manipulate them using the continuous-time

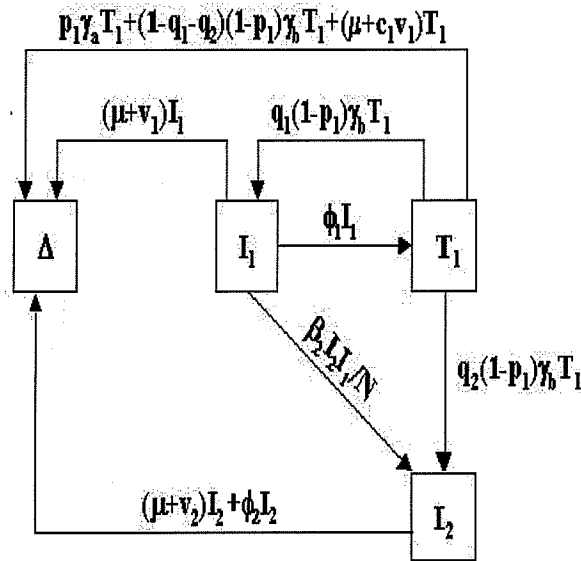


Figure 2: Absorbing state model

Markov chain process outlined in [4] (see appendix for further computation). This gives us the vector  $\Pi$  relating to  $R_0^{[1]}$  and  $\hat{\Pi}$  relating to  $R_0^{[2]}$ . Next, we calculate  $\delta_{ij}$ , the transition rate from state  $i$  to state  $j$ , for each state in our model. Note that we only consider  $i \neq j$  since  $i = j \Rightarrow \delta_{ij} = 0$ . Using these rates we input the transition probabilities,  $p_{ij} = \frac{\delta_{ij}}{\sum_j \delta_{ij}}$ , for each state into a  $4 \times 4$  matrix [4] (see Equations (1) and (2)). Notice that  $\delta_{I_1 I_2} = 0$  because we neglect the superinfection in our model at the beginning of the epidemic. Assuming initial conditions of the infectious states are small, we see that for large  $N$ ,  $\frac{I_1 I_2}{N}$  is approximately zero. Hence, we feel justified in ignoring superinfection and leave that case for future research. In addition, we assume that  $\gamma_a = \gamma_b$  which simplifies the calculation of  $R_0^{[1]}$ , but does not affect  $R_0^{[2]}$ . In section (5), we consider a more realistic simulation where  $\gamma_b \geq \gamma_a$ .  $P_{I_1}$ , the transition matrix for  $R_0^{[1]}$  is



$$\begin{matrix} & I_1 & T_1 & I_2 & \Delta \\ I_1 & \left( \begin{array}{cccc} 0 & \frac{\delta_{I_1 T_1}}{\delta_{I_1 T_1} + \delta_{I_1 \Delta}} & 0 & \frac{\delta_{I_1 \Delta}}{\delta_{I_1 T_1} + \delta_{I_1 \Delta}} \\ \frac{\delta_{T_1 I_1}}{\delta_{T_1 I_1} + \delta_{T_1 I_2} + \delta_{T_1 \Delta}} & 0 & \frac{\delta_{T_1 I_2}}{\delta_{T_1 I_1} + \delta_{T_1 I_2} + \delta_{T_1 \Delta}} & \frac{\delta_{T_1 \Delta}}{\delta_{T_1 I_1} + \delta_{T_1 I_2} + \delta_{T_1 \Delta}} \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 \end{array} \right) & & & \\ T_1 & & & & \\ I_2 & & & & \\ \Delta & & & & \end{matrix} \quad (1)$$

Likewise,  $P_{I_2}$ , the transition matrix for  $R_0^{[2]}$ , is

$$\begin{matrix} & I_1 & T_1 & I_2 & \Delta \\ I_1 & \left( \begin{array}{cccc} 0 & \frac{\delta_{I_1 T_1}}{\delta_{I_1 T_1} + \delta_{I_1 \Delta}} & 0 & \frac{\delta_{I_1 \Delta}}{\delta_{I_1 T_1} + \delta_{I_1 \Delta}} \\ \frac{\delta_{T_1 I_1}}{\delta_{T_1 I_1} + \delta_{T_1 I_2} + \delta_{T_1 \Delta}} & 0 & \frac{\delta_{T_1 I_2}}{\delta_{T_1 I_1} + \delta_{T_1 I_2} + \delta_{T_1 \Delta}} & \frac{\delta_{T_1 \Delta}}{\delta_{T_1 I_1} + \delta_{T_1 I_2} + \delta_{T_1 \Delta}} \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{array} \right) & & & \\ T_1 & & & & \\ I_2 & & & & \\ \Delta & & & & \end{matrix} \quad (2)$$

where the transition rates for these matrices are

$$\begin{aligned}
\delta_{I_1 T_1} &= \phi_1 \\
\delta_{I_1 \Delta} &= \mu + v_1 \\
\delta_{I_2 T_2} &= \phi_2 \\
\delta_{I_2 \Delta} &= \mu + v_2 \\
\delta_{T_1 I_1} &= q_1(1 - p_1)\gamma_b \\
\delta_{T_1 I_2} &= q_2(1 - p_1)\gamma_b \\
\delta_{T_1 \Delta} &= p_1\gamma_a + (1 - q_1 - q_2)(1 - p_1)\gamma_b + \mu + cv_1
\end{aligned}$$

### 3.3 Calculation of $R_0^{[1]}$ and $R_0^{[2]}$

To calculate  $R_0^{[1]}$  which is the number of secondary infectious caused by a single infectious individual in  $I_1$ , we first assume that every infection starts in  $I_1$ . Then in the last row of the transition matrix  $P_{I_1}$ , state  $\Delta$  communicates with state  $I_1$  with probability 1. Let  $E[Z_j^{(i)}]$  be the expected time spent in state  $j$  before going to state  $\Delta$  when starting in state  $i$ . In our model, the average number of infections caused by an individual starting in  $I_1$  includes the expected time spent in either or both infectious states before complete recovery or death. Since we deal with the possibility

of becoming infected with strain 2 when an individual fails to complete treatment,  $R_0^{[1]}$  may consist of secondary infected individuals from both  $I_1$  and  $I_2$ . Thus,

$$R_0^{[1]} = \beta_1 E[z_{I_1}^{(I_1)}] + \beta_2 E[z_{I_2}^{(I_1)}]. \quad (3)$$

Using the transition matrix  $P_{I_1}$  and the Markov chain process [4], we find the stationary distribution

$$\Pi = [\pi_{I_1}, \pi_{T_1}, \pi_{I_2}, \pi_{T_2}, \pi_{\Delta}]$$

in order to calculate  $E[Z_j^{(I_1)}]$ . In analyzing the vector  $\Pi$ , the first element,  $\pi_{I_1}$ , represents the proportion of visits made to state  $I_1$ . The fifth element,  $\pi_{\Delta}$ , displays the proportion of visits made to the absorbing state. Dividing  $\pi_{I_1}$  by  $\pi_{\Delta}$  reveals the total number of visits to  $I_1$  between two visits to  $\Delta$ . A similar calculation is made for  $\frac{\pi_{I_2}}{\pi_{\Delta}}$ . Multiplying these values by the average amount of time spent in the respective infectious state during each visit gives us  $E[Z_j^{(I_1)}]$ , the expected time spent in state  $j$  before absorption when the first infected individual starts in state  $I_1$ . By definition [4],

$$E[Z_j^{(i)}] = \frac{\pi_j}{\pi_{\Delta} \delta_j}$$

where  $\delta_j$  is the rate at which an individual leaves state  $j$ . In other words,  $\frac{1}{\delta_j}$  is the average time spent in state  $j$ . So  $\frac{1}{\delta_{I_1}} = \frac{1}{\phi_1 + \mu + v_1}$  and  $\frac{1}{\delta_{I_2}} = \frac{1}{\phi_2 + \mu + v_2}$ . Substituting these values into (1),

$$R_0^{[1]} = \beta_1 \frac{\pi_{I_1}}{\pi_{\Delta} \delta_{I_1}} + \beta_2 \frac{\pi_{I_2}}{\pi_{\Delta} \delta_{I_2}} \quad (4)$$

$$\Rightarrow R_0^{[1]} = \frac{\beta_1(\gamma_1 + \mu + c_1 v_1)(\phi_2 + \mu + v_2) + \beta_2 q_2 \phi_1 \gamma_1 (1 - p_1)}{(\phi_1 + \mu + v_1)(\gamma_1 + \mu + c_1 v_1 - q_1 \phi_1 \gamma_1 (1 - p_1))(\phi_2 + \mu + v_2)}. \quad (5)$$

Now, the calculation of  $R_0^{[2]}$  involves the assumption that every infection starts in  $I_2$ . In the transition matrix  $P_{I_2}$ ,  $\Delta$  interacts with  $I_2$  with probability 1. Thus, the average number of secondary infections caused by an individual starting in  $I_2$  is

$$R_0^{[2]} = \beta_1 E[Z_{I_1}^{(I_2)}] + \beta_2 E[Z_{I_2}^{(I_2)}] \quad (6)$$

$$\Rightarrow R_0^{[2]} = \beta_2 E[Z_{I_2}^{(I_2)}]. \quad (7)$$

This definition comes from the impossibility of becoming infected with strain 1 when every infection starts as strain 2, hence  $E[Z_{I_1}^{(I_2)}] = 0$ . Using the transition matrix  $P_{I_2}$  and the Markov chain analysis [4] to find the stationary distribution

$$\hat{\Pi} = [\hat{\pi}_{I_1}, \hat{\pi}_{T_1}, \hat{\pi}_{I_2}, \hat{\pi}_{T_2}, \hat{\pi}_{\Delta}],$$

we calculate  $E[Z_{I_2}^{(I_2)}]$  and substitute it into (5). Therefore,

$$R_0^{[2]} = \beta_2 \frac{\hat{\pi}_{I_2}}{\hat{\pi}_{\Delta} \delta_{I_2}} \quad (8)$$

$$\Rightarrow R_0^{[2]} = \frac{\beta_2}{\phi_2 + \mu + v_2}. \quad (9)$$

### 3.4 Probability of Extinction

Once we have the values of  $R_0^{[I_1]}$  and  $R_0^{[I_2]}$ , the probability of extinction for each strain becomes an easy computation. Let  $P_e^{(I_1)}$  be the probability of extinction of strain 1 and  $P_e^{(I_2)}$  be that of strain 2. Then the probability that both strains go to extinction,  $P_e^*$ , is  $P_e^{(I_1)} P_e^{(I_2)}$ . We use the definition of probability of extinction for strain  $i$  given in [4],  $P_e[i] = \frac{1}{R_0^{[i]}}$ . However, this assumes only one infected class for one strain of bacteria. We extend the definition to our model, including two infectious states for two bacterial strains and finding the probability of extinction for each strain. Therefore,

$$P_e^{(I_1)} = \frac{1}{R_0^{[1]}} = \frac{1}{\beta_1 E[z_{I_1}^{(I_1)}] + \beta_2 E[z_{I_2}^{(I_1)}]} \quad (10)$$

$$\Rightarrow P_e^{(I_1)} = \frac{(\phi_1 + \mu + v_1)(\gamma_1 + \mu + c_1 v_1 - q_1 \phi_1 \gamma_1 (1 - p_1))(\phi_2 + \mu + v_2)}{\beta_1 (\gamma_1 + \mu + c_1 v_1)(\phi_2 + \mu + v_2) + \beta_2 q_2 \phi_1 \gamma_1 (1 - p_1)} \quad (11)$$

$$P_e^{(I_2)} = \frac{1}{R_0^{[2]}} = \frac{1}{\beta_2 E[Z_{I_2}^{(I_2)}]} \quad (12)$$

$$\Rightarrow P_e^{(I_2)} = \frac{\phi_2 + \mu + v_2}{\beta_2} \quad (13)$$

Thus,

$$P_e^* = \frac{(\phi_1 + \mu + v_1)(\gamma_1 + \mu + c_1 v_1 - q_1 \phi_1 \gamma_1 (1 - p_1))(\phi_2 + \mu + v_2)^2}{\beta_1 \beta_2 (\gamma_1 + \mu + c_1 v_1)(\phi_2 + \mu + v_2) + (\beta_2)^2 q_2 \phi_1 \gamma_1 (1 - p_1)} \quad (14)$$

Note that  $R_0^{[i]}$  takes on a different meaning from a one-strain model because we cannot determine which of the two strains infects a typical individual. We do not have a definition for a general  $R_0$ . Hence,  $P_e^*$  is only an approximation.

## 4 Analyzing the probability of extinction

In order to determine the significance of the probability of extinction values obtained in Section 3, we create a number of three dimensional plots. Since we are interested in examining the effects of antibiotic misuse on the rise of resistance, we focus on the parameters that describe misuse,  $p_1$ ,  $q_1$ , and  $q_2$  in our analysis. Because the probability of extinction of strain 2 is not influenced by these values, we examine it in terms of  $\beta_2$  and  $\phi_2$ .

### 4.1 Selecting Parameter Values

Before the three dimensional plots can be made it is necessary to select fixed numerical values for those parameters which will not be varied. A review of numerous studies has enabled us to select the following values (the sources are given below). However, when considering these numbers it is important to note that we expect them to be no more than rough approximations. In many cases, they were borrowed from studies which did not focus primarily on obtaining them. Thus, the methods by which they were originally calculated may lack rigor. Nonetheless, they will suffice to demonstrate the general behavior of our system. Note, all parameter values have units  $(years)^{-1}$  unless otherwise noted.

$\mu$  - 0.0133. The life expectancy of an average person in the United States is 75 years

[15], so,  $\frac{1}{\mu} = 75 \Rightarrow \mu = \frac{1}{75} = 0.0133$ .

$\alpha$  - 0.0117. The population of the U.S. is increasing by 1.17% annually [19]. So,  $(\alpha - \mu) = 0.0117 \Rightarrow \alpha = .0133 + \mu = 0.0133 + 0.0117 = 0.025$ .

$c_1$  - 0.1. Antibiotic treatment of bacterial pneumonia has reduced disease induced morbidity by 90%, [20]. So,  $c_1 v_1 = v_1 - .9v_1 \Rightarrow c_1 v_1 = (1 - .9)v_1 \Rightarrow c_1 = 0.1$ .

$\gamma_a$  - 36.5. A typical antibiotic treatment of bacterial pneumonia lasts 10 days, [16]. If the expected duration of treatment is  $\frac{1}{\gamma_a} = 10 \text{ days} = 0.0274 \text{ years}$  then,  $\gamma_a = \frac{1}{0.0274} = 36.5$ .

$\gamma_b$  - 52. VanFleet [12], estimates that individuals who do not complete antibiotic therapy for bacterial pneumonia typically stop treatment after seven days, when symptoms have fully abated. The expected duration of treatment for these individuals is thus,  $\frac{1}{\gamma_b} = 7 \text{ days} = 0.0192 \text{ years}$ , so  $\gamma_b = 52$ .

$q_1$  - 0.07. The probability that an individual with bacterial pneumonia will experience a recurrence of the disease is 7% [7].

We were unable to find consistent and accurate values for the remaining parameters in the biological literature. When possible we estimate them using available biological data. In other cases we base our approximations on the relationships these parameters should have with respect to other known parameters. Through a series of simulations and adjustments we obtain the following values for which strain 1 will be able to sustain itself consistently in the presence of strain 2 for up to seven years (the longest period of time we consider). We feel this condition is requisite for accepting these values because a model in which strain 1 cannot exist in the presence of strain 2 for an extended period of time under normal conditions will not accurately reflect the true behavior of the system. We find:

$\beta_1$  - 146. This value indicates that a person in the non-resistant infectious state ( $I_1$ ) causes 0.4 infections per day, or approximately 2 infections every five days.

$\beta_2$  - 82. This implies that a person in the resistant infectious state ( $I_2$ ) will infect 0.23 persons per day, just over one person every five days. This value is biologically correct in that it reflects the less invasive, more virulent character of  $\beta_2$ .

- $v_1$  - 0.15. Roughly thirty percent of untreated pneumonia cases result in death, [6]. However, through numerical simulation we found that the most realistic outcomes were obtained only when disease induced mortality was around 0.15.
- $v_2$  - 0.2. We expect strain 2 to cause death more frequently than strain 1 due to the fact that strain 1 is more invasive, however less virulent, while strain 2 is less invasive and more virulent.
- $c_2$  - 0.9. Treating penicillin resistant strains of *S. pneumoniae* with penicillin will not significantly reduce the impact of the infection on the carrier. We expect that treatment will not significantly reduce disease induced mortality and so estimate this value.
- $\phi_i$  - 73. Symptoms of bacterial pneumonia may appear between 12 hours and 2 weeks after infection [9]. We found that 5 days provided realistic results. We expect individuals will seek treatment when symptoms surface, so  $\frac{1}{\phi_1}$ , the expected time until individuals move from  $I_1$  to  $T_1$ , is 5 days = 0.0137 years. If  $\frac{1}{\phi_1} = 0.0137$ , then  $\phi_1 = 73$ .
- $\phi_2$  - 73. Resistance to penicillin will not change the rate at which bacteria multiply. We thus assume that symptoms will appear at the same rate in those infected with resistant and non-resistant strains.
- $\gamma_2$  - 20. Treatment of the resistant strain will be relatively ineffective and should take a longer period of time than treating the non-resistant strain. Through trial and error we found that a value of 20 gives realistic results. This value represents an 18 day treatment period.
- $p_1$  -  $\frac{1}{3}$ . Physicians [9] estimates that  $\frac{1}{3}$  to  $\frac{3}{4}$  patients with bacterial pneumonia complete their treatment. We found that a value of  $\frac{1}{3}$  provided more realistic results for patients with strain 1.
- $p_2$  -  $\frac{3}{4}$ . If  $\frac{3}{4}$  of patients with strain 2 complete treatment realistic results are obtained.
- $q_2$  - 0.01. We estimated that the probability that an individual infected with strain 1 will develop strain 2 as a result of incomplete treatment is very low.

## 4.2 Numerical Analysis of the Probability of Extinction

First, we analyze the probability that strain 1 will go extinct in terms of  $q_1$ , the probability that an individual who does not complete treatment goes back to strain 1, and  $q_2$ , the probability that an individual who does not complete treatment goes back to strain 2. We find that when  $q_1$  and  $q_2$  are both zero the probability of extinction is largest,  $\frac{1}{2}$ . When  $q_2$  is one, then the probability of extinction of strain 1 is lower, therefore strain 1 benefits from secondary infections in  $I_2$ . Thus, it is best for strain 1 if they go back to  $I_1$ , it is next best if they go to  $I_2$ , and it is not so good if they go back to  $S$ . We think the reason for this strange behavior where strain 1 benefits from causing secondary infections in strain 2 has to do with the difficulty of defining a single strain  $R_0$  in a two strain stochastic model. Strain 1 prefers to have individuals from  $T_1$  go back to  $I_1$  because they can infect other people. If this behavior is repeated then the probability of extinction of strain 1 is almost zero because we have a cycle between  $I_1$  and  $T_1$ .

Next we analyze the probability of extinction of strain 1 in terms of  $p$  and  $q_1$ . The highest probability of extinction is 0.5 when  $p = 1$  which means that everyone takes their medication. When this happens  $q_1$  has no effect over the individuals. Thus, everyone becomes susceptible and they can not go back to strain 1 and infect other individuals. As  $p$  decreases,  $q_1$  has more influence over the probability of extinction. When the values of  $q_1 = 1$  and  $p = 0$ , the  $Pe^{(I_1)}$  is zero. So, as the probability of  $p$  increases  $Pe^{(I_1)}$  increases. We also analyzed the  $Pe^{(I_1)}$  in terms of  $q_2$  and  $p$ . The values of  $q_2$  do not affect  $Pe^{(I_1)}$  as much as the values of  $q_1$ . For example even when  $p = 0$  and  $q_2 = 1$  the  $Pe^{(I_1)}$  is 0.3. This tells us that  $q_2$  is not a strong factor in the  $Pea^{(I_1)}$ . Aside from this difference,  $q_2$  causes the same kind of behavior as when we analyzed  $q_1$  and  $p$ .

Now we analyze the same probability only with  $\phi_1 = 155$  (2.35 days before an individual seeks treatment). The results are generally the same but when people look for treatment after 2.5 days the disease will definitely go extinct for low values of  $q_1$  and high values of  $p$  (see Figure 3). Also, when  $p = 1$  strain 1 will go extinct for any value of  $q_1$ . When we analyze the  $Pea^{(I_1)}$  in terms of  $p$  and  $\phi_1$  we see that for every value of  $\phi_1$  greater than 160 (2.28 days before an individual seeks treatment) the disease always goes to extinction.

Next we analyze the probability of extinction of strain 2 in terms of  $\phi_2$  and  $\beta_2$ . We choose these parameters because the  $Pe^{(I_2)}$  does not depend on  $p$ ,  $q_1$  and  $q_2$ . We notice that having our parameters  $\beta_2 = 81.76$  and  $\phi_2 = 73$  the disease has a very

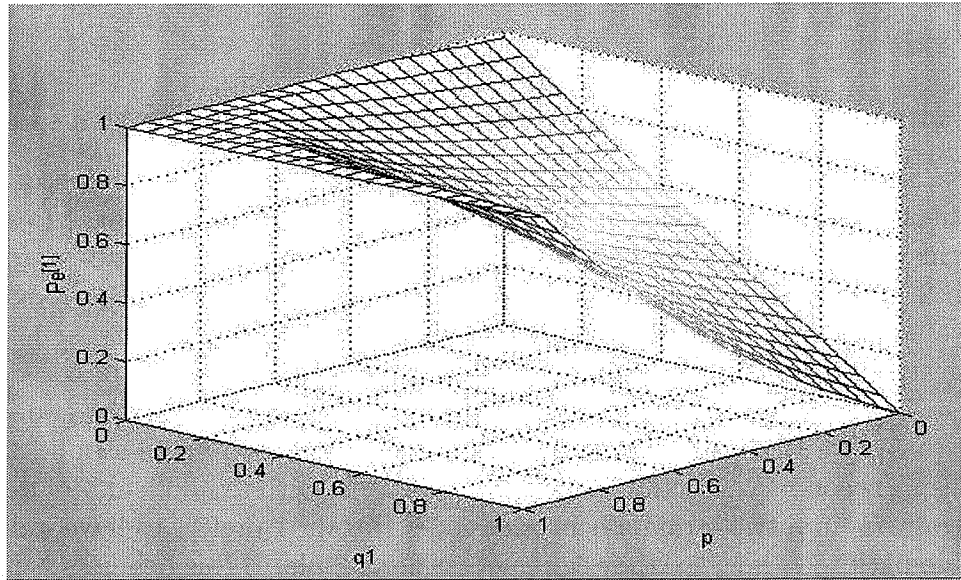


Figure 3: Probability of extinction of strain 1

high probability of extinction. When  $\beta_2 < \phi_2$  we find that strain 2 will always go to extinction. In general, it looks like  $Pe^{(I_2)}$  goes to one when  $\beta_2$  approximately equals  $\phi_2$ . In order for strain 2 to sustain itself  $\beta_2$  has to be greater than  $\phi_2$  (see Figure 4).

Now we analyze the probability of extinction of both strains,  $Pe^*$ . When the values of  $q_1$  and  $q_2$  are equal to one,  $Pe^*$  is almost zero. This is because more people are getting infected with both strains. But we also notice that  $Pe^*$  will dramatically increase when less people are becoming infected with strain 1. In these cases  $q_2$  does not have as much influence as  $q_1$  on  $Pe^*$ .

When the value of  $q_1$  decreases and  $p$  increases the probability of extinction of both strains will increase to a maximum of 0.45. Thus,  $Pe^*$  is largest when more individuals finish their medication and less individuals who do not finish their medication become infected with strain 1. If the probability that an individual takes their medication is almost zero and a large number of individuals become infected with strain 1 as a result, then the  $Pe^*$  will be almost zero. This behavior relates to  $Pea^{(I_1)}$  where  $p$ ,  $q_1$  and  $q_2$  affect  $Pe^*$  in the same way, this happens because the  $Pe^{(I_2)}$  does not depend on either of these parameters. Thus under these conditions multiplying  $Pe^{(I_1)}$  by  $Pe^{(I_2)}$  is equivalent to multiplying it by a constant and changes only the slope of the graph, not its overall behavior (see Figure 5).



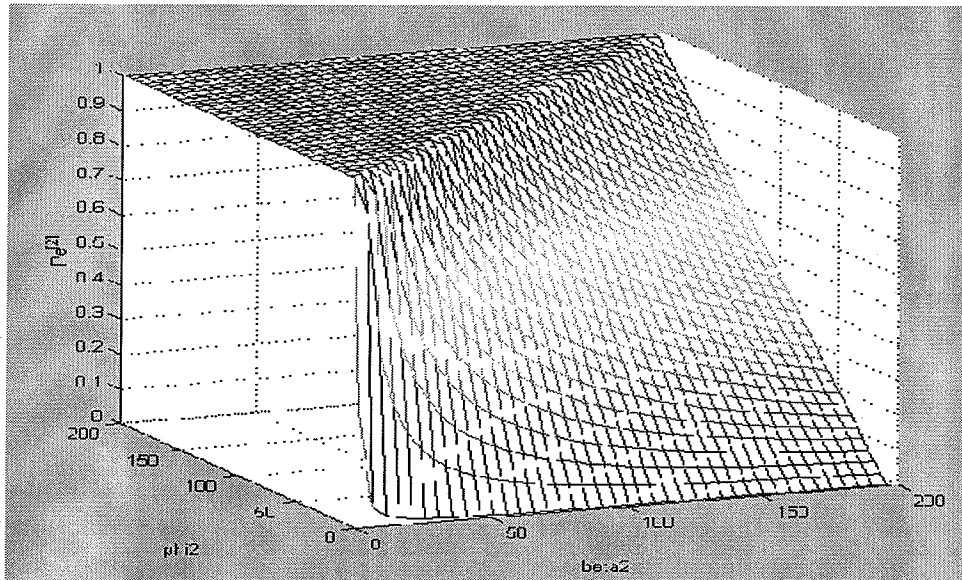


Figure 4: Probability of extinction of strain 2

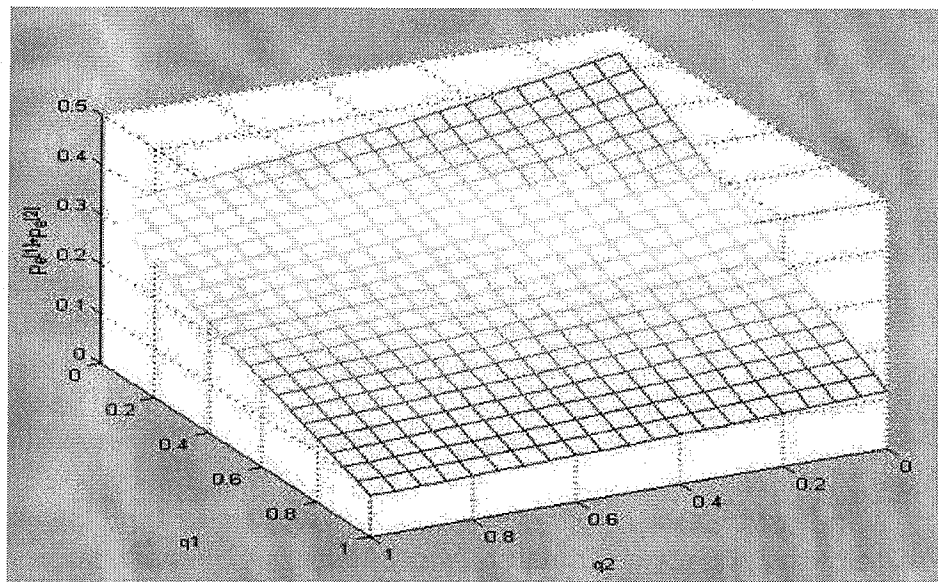


Figure 5: Probability of extinction both strains

## 5 Stochastic Simulations and Results

We simulate the existence and evolution of bacterial strain 1 and strain 2 introduced to a population of susceptible individuals using Matlab. Plotting the number of individuals in  $I_1$  and  $T_1$  versus time on one graph and the number of individuals in  $I_2$  and  $T_2$  versus time on another graph allows us to compare the behavior and lifespan of each strain. In our stochastic simulations we use the parameter values listed in section (4.1) unless otherwise noted.

By varying the probability that an individual completes antibiotic treatment, we take note of the relationship between the two strains over time. Since we assume that strain 1 is non-resistant and strain 2 is resistant to antibiotics, it appears that the probability that an individual infected with strain 1 finishes treatment directly influences the survival of strain 1 and indirectly influences the survival of strain 2. Through simulations, we find parameter ranges for coexistence, short-term domination of strain 2 after the extinction of strain 1, and simultaneous extinction of both strains. First, coexistence of the two strains occurs when  $p_1 < 0.8$ . This means that if less than 80% of people infected with strain 1 complete their medication,  $I_2$  sustains a small endemic population with periodic outbreaks. This situation has the potential to become a problem because one of the outbreaks, shown as a peak in the graph of  $I_2$  versus time, could jump above  $I_1$  and cause an epidemic. Then strain 2 would get the chance to take over as strain 1 goes extinct (see Figure 6). Now, when  $p_1 \geq 0.8$ , the resistant strain briefly overtakes the non-resistant strain, but dies out shortly thereafter. So we see that both strains eventually go extinct and most likely will not cause a significant problem when more than 80% of the individuals in  $I_1$  complete treatment. Also, we note that as  $p_1$  increases to 1 from this value, it takes less time on average for strain 2 to die out. At  $p_1 = 1$ ,  $I_2$  dies out almost immediately which makes sense because if everyone in  $I_1$  finishes their medication, they all go back to being susceptible, and hence, superinfection decreases dramatically (see Figure 7). Conversely, when  $p_1 = 0$ , the two strains coexist for a short time (less than one year) and die out together. We observe that strain 2 needs a constant or periodic influx from strain 1 to survive. While everyone fails to complete treatment, without the presence of strain 1, strain 2 cannot sustain itself and inevitably goes extinct. Here we must note that the critical value of  $p_1 = 0.8$  only applies to this specific set of parameters. Varying virulence or per capita rate of contact may shift this value.

Next, we vary the parameters  $q_1$  and  $q_2$  which represent the probabilities that an individual being treated for strain 1 remains infected or acquires strain 2, respectively, when treatment is not completed. Similar to the previous simulations varying  $p_1$ , we find ranges for  $q_1$  and  $q_2$  where the two strains coexist. While  $q_1 > 0.1$  and  $q_2 < 0.01$

we see strong coexistence for long periods of time interjected with short, periodic outbreaks of strain 2. Over a seven year time scale, we find strain 2 dominating strain 1 for several brief periods and then receding to its low endemic population size. A greater  $q_1$  value means more people go back to state  $I_1$  after stopping treatment. Thus, an increased flow to  $I_1$  easily sustains strain 2. This behavior is similar to that under our standard parameter values (see Figure 6). Increasing  $q_1$ , we notice that the time between outbreaks of strain 2 decreases (see Figure 8). On the other hand, increasing  $q_2 > 0.01$  can disrupt  $I_1$  and cause accelerated probabilities of extinction of both strains with a short peak of strain 2 before extinction. Combining high  $q_2$  and low  $p_1$  values, we also see increases in the frequency of periodic outbreaks or peaks in  $I_2$ , ending with simultaneous extinction of both strains (see Figure 9). Thus, a higher probability that an individual infected with strain 1 moves to  $I_2$  along with very few people finishing their medication results in more strain 2 outbreaks over time.

Lastly, we vary the virulence of each strain, how fast the bacteria is able to kill its host, and note other miscellaneous results. By increasing the values of  $v_1$  and  $v_2$  at the same rate, we observe coexistence with small, periodic outbreaks until strain 1 goes extinct. At that point, strain 2 peaks quickly and drastically before dying out (see Figure 10). Under increased virulence and as  $q_2$  increases to 1,  $I_2$  appears to decrease over time. Coexistence and periodic cycles still occur, but we notice a potential for strain 1 to die out and strain 2 to slowly take over. Now we consider the effect  $\beta_2$ , the per capita contact rate, and virulence have on each strain. Increasing  $\beta_2$ ,  $v_1$ , and  $v_2$  makes strain 2 more able to invade its host and both strains able to kill faster. Hence, strain 2 exists for a longer period after strain 1 goes extinct (see Figure 11).

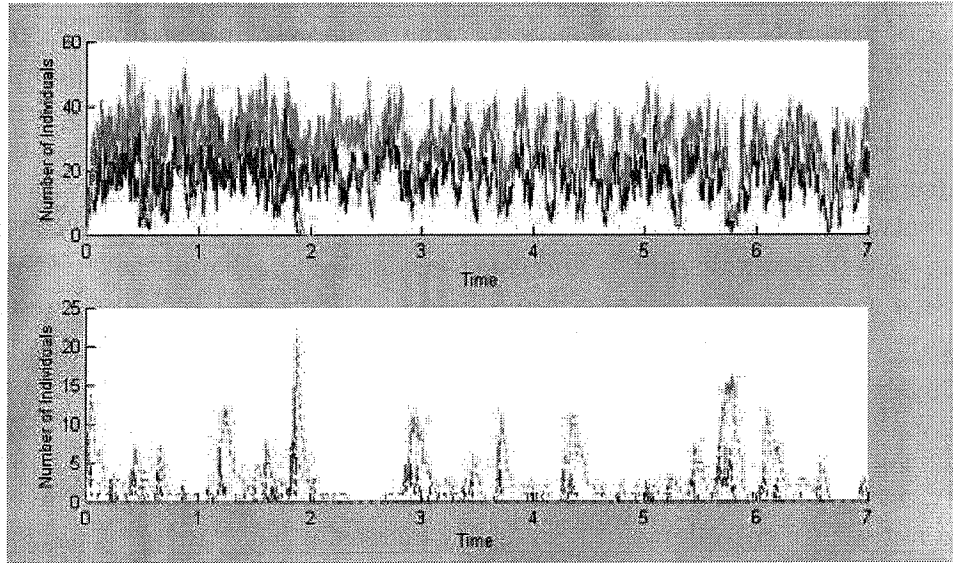


Figure 6: Coexistence under standard conditions where  $I_2$  sustains a small endemic population,  $p_1 = 0.33$ .

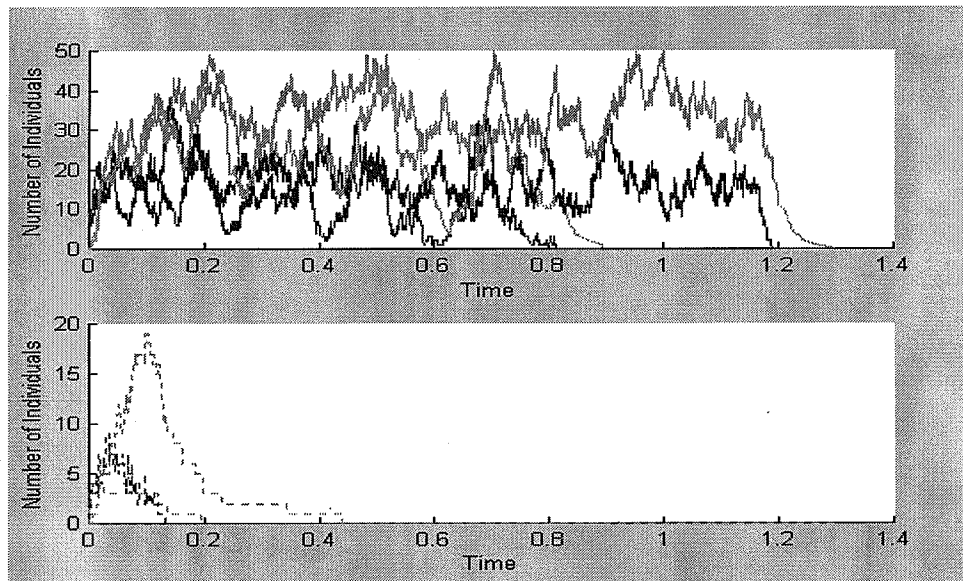


Figure 7: Strain 2 dies out quickly when everyone completes treatment,  $p_1 = 1$ .

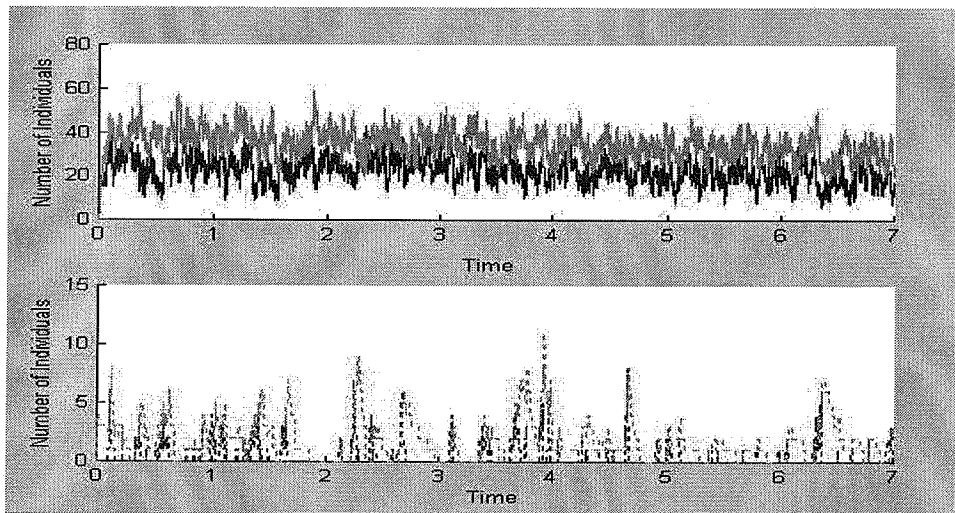


Figure 8: Increasing  $q_1$  causes an increase in the frequency of strain 2 periodic outbreaks,  $q_1 = 0.45$ .

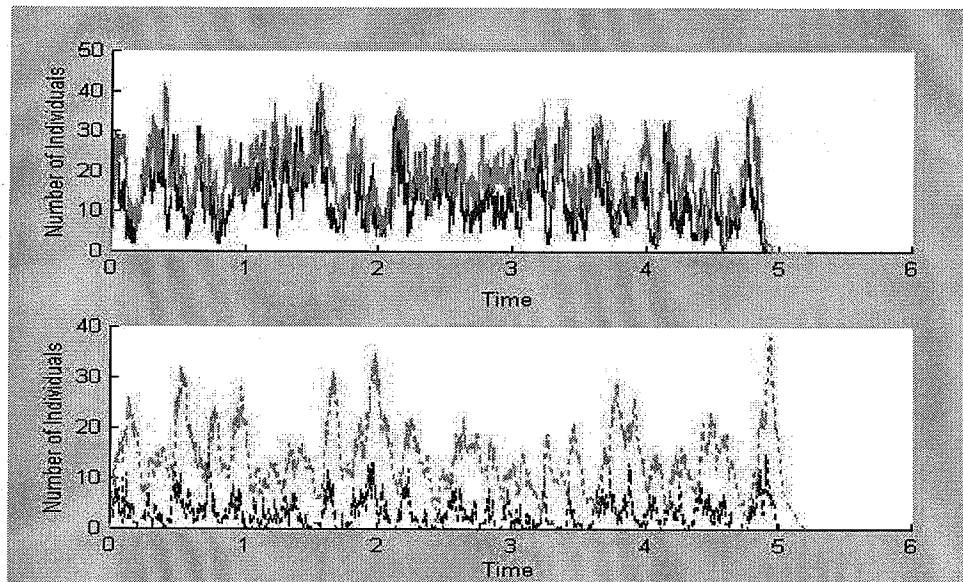


Figure 9: Increased frequency of strain 2 periodic outbreaks and simultaneous extinction of both strains,  $q_2 = 0.075$  and  $p_1 = 0.001$ .