Coinfection and the Evolution of Resistance: A Mathematical Analysis

by
Johanna J. H. Hansen

A thesis submitted to the Department of Mathematics and Statistics

in conformity with the requirements for

the degree of Master of Science

Queen's Univeristy

Kingston, Ontario, Canada

April 2011

ABSTRACT

This thesis investigates the effect of coinfection on the emergence of resistant pathogens. Firstly, a multiple infection model with treatment is derived and the conditions for invasion are established. The invasion condition is then related to an equivalent and easier to obtain condition, R_0, by applying the Next-Generation Theorem. Due to its biological interpretation, a heuristic derivation of R_0 as the invasion condition is also given. Then assuming that resistance comes at a cost to the pathogen, and using a very simple within-host model, we establish under which specific set of biological assumptions we should expect coinfection to increase or decrease R_0. Specifically, we obtain that in the no cost of resistance case, reduced transmission case, and increased mortality case, that coinfection will increase the R_0 value and that in the reduced growth and poor competitor case that the effect is indeterminate. We also introduced a method for approximating the intrinsic growth rate when the coinfection efficiency is assumed to be small. Using this method, we show that we obtain the same trend for the cost of resistance cases when comparing our estimate for the intrinsic growth rate for the coinfection case versus the intrinsic growth rate for the single infection case. We also use this approximation to estimate the percentage of resistance as a function of time. Finally, we analyze how both the intrinsic growth rate and R_0 respond to a changing treatment rate, compared to the intrinsic growth rate and R_0 value in the single infection case. We found that the change in R_0 and the intrinsic growth rate can be greater or smaller than the change

in R_0 or the intrinsic growth rate for the single infection case.

To my boyfriend, my family, my friends and my pets. You make life more fun.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. Troy Day for providing me with the opportunity to write this thesis, his guidance during the inset of this research and for all the time he spent reading and editing various versions of this thesis. Without your constant support, this thesis would not have been nearly as good, and it would likely contain many more typos. I would like to thank Dr. Andrew Read, of Penn State University, for providing much of the biological motivation for this work as well as for his contagious enthusiasm for science. I would like to thank my committe members, especially Dr. Peter Taylor and Dr. William Nelson for insightful comments and corrections. I would also like to acknowledge the enriching environment provided by the Queen's Mathematical Biology Group, the Queen's department of Mathematics and Statistics, and the Queen's Biology department. I would also like to thank the staff of the Queen's department of Mathematics and Statistics especially Jennifer Read. I would also like to thank my Jeffery Hall office mates for enlightening mathematical discussions and levity. Also, I would like to thank my friends, boyfriend and family for their support and good cheer. Finally, I would especially like to acknowledge my parents, Jeanette J. Hansen and Don L. Hansen for their love, support and encouragement. You have been exceptional from the beginning.

Table of Contents

List of Tables

List of Figures

CHAPTER I

Introduction

With advances in genotyping technology we are now aware that many microparasite infections are made up of more than one genotypically distinct clonal lineage [16]. This has been described for many types of diseases including *Mycobacterium turberculosis* [7], Eppstein Bar Virus [18] and Malaria [2] to list but a few. Surely one could hypothesize that the genetic diversity of an infection and intervention strategies that could alter this diversity, such as drug treatment, would have an effect on the overall host ecology. This in turn could have a potential effect on the severity and progression of a disease as well as the spread and emergence of pathogens that are resistant to treatment. For example, if a resistant, to treatment, strain is being competitively suppressed by a sensitive strain, within a host, then drug treatment could result in competitive release of the resistant strain. This could mean that when multiple infections are present within a host, resistant strains will spread much quicker than if only single infections occurred [9]. In fact in the rodent malaria model, *P. chabaudi* experiments have shown that competitive release does occur [21][5].

Despite the increasing experimental evidence regarding the existence and potential importance of multi-clonal infections, theoretical work still largely ignores this entanglement. In fact, the majority of mathematical models assume that a host can

be infected with only one clonal type of pathogen. Certainly, depending on the type of biological question this may be sufficient; however in some cases we contend it is not. Some models do not ignore the multiple infection scenario completely but instead use the simplifying scenario termed "superinfection". Superinfection, coined by Nowak and May [13] allows for multiple infections; however it assumes that the more virulent strain will supersede the less virulent strain, on a time scale which is assumed to be fast relative to the epidemiological dynamics of interest. In some cases, this assumption may be correct but certainly one could imagine that cases may arise where the competitive advantage of one strain over another is small and/or time scale of interest is not sufficiently long enough to assume that one strain will dominate over the other.

Van Baalen and Sabelis [20] explored this "coinfection" scenario where up to two strains are allowed to infect a host at one time and both strains can contribute to host mortality and transmission. Under this scenario, they show that more virulent strains may be selected for when pathogens could potentially have to share their hosts. Recently, Alizon and van Baalen [1] combined a within-host immune dynamics model with a coinfection model to study the implications of immunity and multiple infections on virulence evolution.

Using the same theoretical framework as van Baalen and Sabelis [20] we model the emergence of drug resistant pathogens under drug treatment pressure. Drug resistance is both a major financial and human cost concern and it is not limited to the widely publicized antibiotic resistance but is of major concern for all sorts of pathogens including bacteria, fungi, malaria and viruses [17]. Modeling the emergence of resistant pathogens has certainly been an active field of research. However mathematical models that incorporate the effect of multiple infections in the emer-

gence of resistant pathogens to date has been largely neglected.

1.1 Organization of Thesis

Chapter 2 begins by laying out the framework for our multiple infection model as well as the conditions for invasion by a resistant pathogen. Applying the Next-Generation Theorem it establishes $R_0 > 1$ as the invasion condition for a resistant pathogen. Chapter 3 looks at the effect of coinfection on the emergence of resistance in a multiple infection model compared to a single infection model. It also explores the time scale of the emergence of resistance by approximating the intrinsic growth rate. In chapter 4 the effect of changing the treatment rate on R_0 and the intrinsic growth rate in the coinfection case is compared to the effect if single infections only were permitted.

CHAPTER II

Multiple Infection Model and Conditions for Invasion

In this chapter, we will begin by devoloping a multiple infection model. We will then perform an invasion analysis, and establish the necessary condition for a resistant strain to invade a population at an endemic equilibrium. We will also derive an equivalent invasion condition by applying the Next-Generation Theorem. This equivalent condition, termed R_0, also has a biological significance and therefore we will also offer a biologically motivated heuristic derivation of R_0.

2.1 Multiple Infection Model

Following a similar method to van Baalen and Sabelis [20] we begin by extending the standard SI (susceptible and infected) model [8] to allow for multiple infections. Like van Baalen and Sabelis' model we consider the simplest case of coinfection by allowing a host to be infected by up to two strains. Let S denote the number of susceptibles and let I_X denote the number of individuals in an infectious class X. Note that we will also sometimes use I_X and S to denote the actual class itself, however this should be clear through context.

Figure 2.1 depicts the flow through infectious classes. Susceptibles, (S), can either be infected with strain A or strain B. After being infected once they can then become additionally infected with strain A or B. This results in 6 different infectious classes,

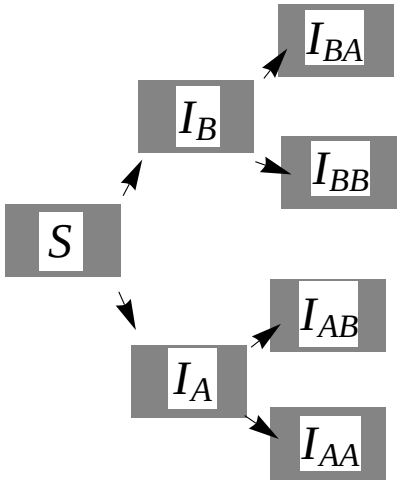

Figure 2.1: Multiple Infection Model

infected with stain A, (I_A), infected with strain B, (I_B), infected with strain A twice or strain B twice, I_{AA} and I_{BB},[1] infected with strain A and then strain B, (I_{AB}), and infected with strain B and then strain A, (I_{BA}). This logic can easily be extended to allow for coinfection of more than two strains.

Susceptibles enter the system at a constant rate Θ. From there they either die at a rate $S\mu$ or become infected at a rate $h_A S$ or $h_B S$, where h_A and h_B are the force of infection of strain A and strain B respectively and are given by equation 2.2 and 2.3. Once entering a single infection class, I_A or I_B, the infected individual can either die at rate $\mu_X I_X$ or become additionally infected with either strain A or

[1]The concept of being doubly infected with the same strain may not, at first, be biologically intuitive. However, the author contends that it is in this construct where much of the predictive power of van Baalen and Sabelis' model lies and where, for example, Adler and Mosquera's model [12] falls short. If we are interested in coinfection with different strains of the same pathogen we are implicitly assuming that the mode of action of the two strains is fundamentally the same. In other words there is nothing "special" about a strain infecting an already infected host. Therefore we must allow for the coinfection of a host regardless of the identity of the resident or infecting strain. Although from a practical perspective we would never refer to someone as being doubly infected with strain A, this could be determined in a controlled laboratory experiment. For example, by fluorescently tagging the second inoculum.

B at a rate of $\sigma I_X h_B$ or $\sigma I_X h_A$. We let σ represent the double infection efficiency. It is the probability of infection per infectious contact with a susceptible versus the probability of infection per infectious contact with an already singly infected individual. If the probability of infection per infectious contact is the same for a singly infected individual as it is for for a susceptible then $\sigma = 1$, if it is greater then $\sigma > 1$ and if it is less then $\sigma < 1$. Once in a double infection class I_X, the individual will eventually exit the class through death at a rate of $\mu_X I_X$. This is described by the following system of differential equations:

$$
\begin{aligned}
\dot{S} &= \Theta - \mu S - h_A S - h_B S \\
\dot{I}_A &= h_A S - \sigma h_A I_A - \sigma h_B I_A - \mu_A I_A \\
\dot{I}_B &= h_B S - \sigma h_B I_B - \sigma h_A I_B - \mu_B I_B \\
\dot{I}_{BB} &= \sigma h_B I_B - \mu_{BB} I_{BB} \\
\dot{I}_{AA} &= \sigma h_A I_A - \mu_{AA} I_{AA} \\
\dot{I}_{AB} &= \sigma h_B I_A - \mu_{AB} I_{AB} \\
\dot{I}_{BA} &= \sigma h_A I_B - \mu_{BA} I_{BA}
\end{aligned} \tag{2.1}
$$

and

$$
h_A = \beta_{A,A} I_A + \beta_{AA,A} I_{AA} + \beta_{AB,A} I_{AB} + \beta_{BA,A} I_{BA} \tag{2.2}
$$

$$
h_B = \beta_{B,B} I_B + \beta_{BB,B} I_{BB} + \beta_{AB,B} I_{AB} + \beta_{BA,B} I_{BA}, \tag{2.3}
$$

where $\beta_{X,Y}$ is the transmission efficiency and has units of $\frac{1}{time}$.

Since we are interested in the emergence of resistant pathogens in a multiple infection model under treatment pressure we now extend our model with the inclusion

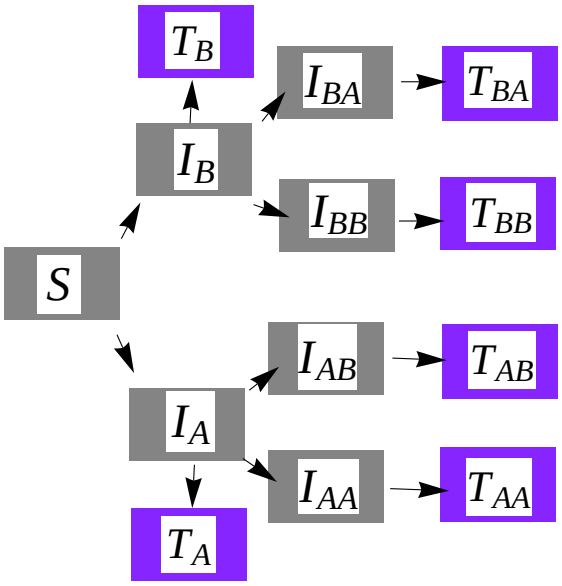

Figure 2.2: Multiple Infection Model with Treatment

of treated classes. Now any infected class can enter a treated class at a constant per capita rate ν. Treated classes can, potentially, infect non-treated classes but we assume that treatment results in reinfection immunity from both pathogens, meaning that treated classes cannot become reinfected. Figure 2.2 depicts the flow through infectious classes to treated classes. This results in the new system of differential equations;

$$
\begin{aligned}
\dot{S} &= \Theta - \mu S - h_A S - h_B S \\
\dot{I}_A &= h_A S - \sigma h_A I_A - \sigma h_B I_A - \mu_A I_A - \nu I_A \\
\dot{I}_B &= h_B S - \sigma h_B I_B - \sigma h_A I_B - \mu_B I_B - \nu I_B \\
\dot{I}_{\mathrm{BB}} &= \sigma h_B I_B - \mu_{\mathrm{BB}} I_{\mathrm{BB}} - \nu I_{\mathrm{BB}} \\
\dot{I}_{\mathrm{AA}} &= \sigma h_A I_A - \mu_{\mathrm{AA}} I_{\mathrm{AA}} - \nu I_{\mathrm{AA}} \\
\dot{I}_{\mathrm{AB}} &= \sigma I_A h_B - \mu_{\mathrm{AB}} I_{\mathrm{AB}} - \nu I_{\mathrm{AB}} \\
\dot{I}_{\mathrm{BA}} &= \sigma I_B h_A - \mu_{\mathrm{BA}} I_{\mathrm{BA}} - \nu I_{\mathrm{BA}} \\
\dot{T}_A &= \nu I_A - \mu_{TA} T_A \\
\dot{T}_B &= \nu I_B - \mu_{TB} T_B \\
\dot{T}_{\mathrm{BB}} &= \nu I_{\mathrm{BB}} - \mu_{TBB} T_{BB} \\
\dot{T}_{\mathrm{AA}} &= \nu I_{\mathrm{AA}} - \mu_{TAA} T_{AA} \\
\dot{T}_{\mathrm{AB}} &= \nu I_{\mathrm{AB}} - \mu_{TAB} T_{\mathrm{AB}} \\
\dot{T}_{\mathrm{BA}} &= \nu I_{\mathrm{BA}} - \mu_{TBA} T_{\mathrm{BA}},
\end{aligned} \tag{2.4}
$$

where we have used the same notational conventions as before, and T_X denotes the number in a treated class X, μ_{TX} is the per capita mortality of treated class X and the forces of infection are now

$$
\begin{aligned}
h_A &= \beta_{A,A} I_A + \beta_{\mathrm{AA},A} I_{\mathrm{AA}} + I_{\mathrm{AB}} \beta_{\mathrm{AB},A} + I_{\mathrm{BA}} \beta_{\mathrm{BA},A} + T_A \beta_{\mathrm{TA},A} \\
&+ T_{\mathrm{AA}} \beta_{\mathrm{TAA},A} + T_{\mathrm{AB}} \beta_{\mathrm{TAB},A} + T_{\mathrm{BA}} \beta_{\mathrm{TBA},A}
\end{aligned} \tag{2.5}
$$

$$
\begin{aligned}
h_B &= \beta_{B,B} I_B + \beta_{\mathrm{BB},B} I_{\mathrm{BB}} + I_{\mathrm{AB}} \beta_{\mathrm{AB},B} + I_{\mathrm{BA}} \beta_{\mathrm{BA},B} + T_B \beta_{\mathrm{TB},B} \\
&+ T_{\mathrm{BB}} \beta_{\mathrm{TBB},B} + T_{\mathrm{AB}} \beta_{\mathrm{TAB},B} + T_{\mathrm{BA}} \beta_{\mathrm{TBA},B}
\end{aligned} \tag{2.6}
$$

where $\beta_{\mathrm{TX},Y}$ is the transmission efficiency of treated class X of pathogen Y.

2.2 Invasion Analysis and Derivation of R_0

Given this multiple infection framework we want to analyze the conditions under which a resistant pathogen will invade a population sensitive to treatment. We will assume that the sensitive strain is at an epidemiological equilibrium prior to the appearance of the mutant, resistant, strain. First we will begin by laying out the general framework for deriving our invasion condition in terms of the equiblibrium of the sensitive strain, under the assumption that this equilibrium is stable in the absence of the mutant, resistant, strain. After we have established this general invasion condition we then layout a specific set of assumptions, II.5 and II.6, below that will allow us to solve for the endemic B equilibrium and the conditions for its local stability.

Let us begin by assuming that strain A is a drug resistant strain and strain B is a drug sensitive strain. Since we are interested in the invasion of strain A, the resistant pathogen, we begin by assuming that there is no strain A in the population, and therefore all quantities involving A in system 2.4 are set to zero.

$$
\begin{aligned}
\dot{S} &= \Theta - \mu S - h_B S \\
\dot{I}_B &= h_B S - \sigma h_B I_B - \mu_B I_B - \nu I_B \\
\dot{I}_{\mathrm{BB}} &= \sigma h_B I_B - \mu_{\mathrm{BB}} I_{\mathrm{BB}} - \nu I_{\mathrm{BB}} \\
\dot{T}_B &= \nu I_B - \mu_{TB} T_B \\
\dot{T}_{\mathrm{BB}} &= \nu I_{\mathrm{BB}} - \mu_{TBB} T_{BB}
\end{aligned}
\tag{2.7}
$$

Assuming that the system is at the endemic equilibrium we introduce a small

amount of strain A infectious material into our system and ask whether or not it will invade the population. This is mathematically equivalent to asking if the endemic B equilibrium of our augmented system 2.4 is stable. In order to evaluate the local stability of this augmented system of ordinary differential equations we calculate the Jacobian of our system at this equilibrium and evaluate the dominant eigenvalue. Let us denote the dominate eigenvalue in the coinfection case by r_C and the dominant eigenvalue in the single infection case, $\sigma = 0$, by r_S. Note, that the dominant eigenvalue is also sometimes referred to as the intrinsic growth rate. If the dominant eigenvalue, r_C, is < 0 then the endemic equilibrium is locally stable. If $r_C > 0$ then the endemic equilibrium is unstable.

To proceed with the analysis we introduce the following definitions:

Definition II.1. $s(G)$

We define $s(G)$ as the spectral abscissa, (maximum real part of the eigenvalues), of a square matrix G.

Definition II.2. $\rho(G)$

We define $\rho(G)$ as the spectral radius, (maximum modulus of the eigenvalues), of a square matrix G.

Definition II.3. Non-singular M-matrix

There are many equivalent definitions of M-matrices. In [3] Berman and Plemmons give 50 equivalent conditions of the statement "G is a non-singular M-matrix". We offer the following: If a matrix $G = [g_{ij}]$ has the Z sign pattern, $g_{ij} \leq 0$ for all i $\neq j$, and if $s(G) > 0$ then G is a non-singular M-matrix.

The Jacobian of equations 2.4, evaluated at the endemic B equilibrium, can be written in the following block triangular form:

$$\begin{pmatrix} J_B & J_1 \\ 0 & J_A. \end{pmatrix} \tag{2.8}$$

where J_B is the Jacobian of our strain B system only and J_A is the Jacobian of system 2.4 without the strain B system. Since this matrix is block triangular its eigenvalues are the eigenvalues of the two diagonal sub-matrices. Furthermore since we have assumed that the endemic equilibrium is stable, $s(J_B) < 0$. Therefore the sign of $s(J_A)$, will completely determine the stability of our system. If $s(J_A) > 0$ then the endemic equilibrium is not stable and we say that the A strain will be able to invade. If $s(J_A) < 0$ then the endemic B equilibrium is locally stable, and the A strain will not be able to invade, at least when rare. Unfortunately, obtaining an expression for $s(J_A)$ requires us to solve for the roots of an 8^{th} order polynomial, because we have equations describing the change in I_A, I_{AA}, I_{AB}, I_{BA}, T_A, T_{AA}, T_{AB}, T_{BA}. However by the Abel-Ruffini theorem we know that for polynomials of degree 5 or higher there is no general algebraic solution [19]. Luckily the condition of whether $s(J_A) < 0$ or $s(J_A) > 0$ is equivalent to looking at another, often easier to evaluate condition. This condition is given by the following theorem:

Theorem II.4. *Next Generation Theorem [15][10]. Let $J_A = F - V$ where V is an M-matrix and $F >= 0$ then*

$$\begin{aligned} s(J_A) < 0 &<=> \rho\left(FV^{-1}\right) < 1 \\ s(J_A) > 0 &<=> \rho\left(FV^{-1}\right) > 1 \\ s(J_A) = 0 &<=> \rho\left(FV^{-1}\right) = 1 \end{aligned}$$

It happens that we can partition the matrix J_A into $J_A = F - V$ where F and V meet the conditions of Theorem II.4 and therefore our stability condition is equivalent to $\rho\left(FV^{-1}\right) < 1$. It further follows that if we choose F and V such that F represents the inflow of new A infections and V represents the transitions through classes, that FV^{-1} can be interpreted as the next-generation matrix. In particular, element ij of FV^{-1} can be interpreted as the expected number of i offspring produced by an individual in class j over its entire lifespan (i.e. per generation). $\rho\left(FV^{-1}\right)$ then has the interpretation of the expected number of secondary propagules produced by a single propagule [20]. Solving for $\rho\left(FV^{-1}\right)$ we obtain:

(2.9)

$$\rho\left(FV^{-1}\right) = \frac{\sigma\hat{I}_B\beta_{\mathrm{BA},A}}{\nu+\mu_{\mathrm{BA}}} + \frac{\hat{S}\beta_A}{\nu+\sigma h_B+\mu_A} + \frac{\hat{S}\sigma\hat{h}_B\beta_{\mathrm{AB},A}}{\left(\nu+\mu_{\mathrm{AB}}\right)\left(\nu+\sigma\hat{h}_B+\mu_A\right)} + \frac{\hat{S}\nu\beta_{\mathrm{TA},A}}{\mu_{\mathrm{TA}}\left(\nu+\sigma\hat{h}_B+\mu_A\right)} + \frac{\hat{S}\nu\sigma\hat{h}_B\beta_{\mathrm{TAB},A}}{\left(\nu+\mu_{\mathrm{AB}}\right)\mu_{\mathrm{TAB}}\left(\nu+\sigma\hat{h}_B+\mu_A\right)} + \frac{\nu\sigma\hat{I}_B\beta_{\mathrm{TBA},A}}{\left(\nu+\mu_{\mathrm{BA}}\right)\mu_{\mathrm{TBA}}}$$

where $\hat{S}$, $\hat{I}_B$ and $\hat{h}_B$ are the values of S, I_B and h_B respectively, at the endemic equilibrium. We present a detailed derivation of 2.9 in appendix A. This quantity is what is commonly referred to in epidemiology as R_0. Since specifically this particular R_0 is the R_0 obtained when coinfection occurs we will refer to it as R_C and the R_0 value when only single infections are permitted we will refer to as R_S. We note that due to its biological interpretation R_C can also be derived in a more heuristic manner. Van Baalen and Sabelis present such a heuristic derivation of R_0, when there is coinfection, for a untreated population [20]. To elucidate the various terms in R_C we will now present a similar heuristic derivation as in [20].

Typically, R_0 is defined as the expected number of secondary infections produced in a completely susceptible population by a typical infected individual [6].

In our case, however, there is more than one kind of infected individual and therefore it is not clear what a "typical" infection would be. One way to get around this is to shift the perspective to that of a propagule newly released into the population, and to ask how many new propagules it is expected to produce. Clearly if an A propagule is expected to produce more than one A propagule on average then the A strain will be expected to invade, (i.e. $R_0 > 1$), and if it produces less than one propagule it will not be expected to invade, (i.e. $R_0 < 1$).

Motivated by the propagule based model found in [4] let us define $\beta_{X,Y}$, the transmission efficiency with units of $(\frac{1}{time})$ in the following manner:

$$\beta_{X,Y} = \frac{b\kappa_{X,Y}}{u} \tag{2.10}$$

where b is defined such that $\hat{S}b$ is the rate at which a propagule encounters and infects susceptibles (S), $\kappa_{X,Y}$ is the rate at which an infected host I_X produces new Y propagules and $\frac{1}{u}$ is the expected lifetime of a propagule.

Now recall our model assumes that a host can become coinfected at a rate that differs from the rate at which it becomes singly infected, where σ is the "correction" factor. In other words $\hat{I}_B\sigma b$ is the rate at which a propagule encounters and infects singly infected classes.

Now, when an A propagule is released into the population it can either infect a host that is singly infected with B, (I_B), or it can infect a susceptible,(S). Therefore we can write R_0 as:

$$R_0 = B_S\hat{S} + B_C\hat{I}_B \tag{2.11}$$

where we will call B_S and B_C the per-host transmission factor and they represent the

total number of propagules produced per I_B host or S type host. B_C is therefore the probability that a propagule infects an I_B host multiplied by the expected number of propagules produced by such an infection, where this incorporates both the number of propagules produced by an I_{BA} infection and the number of propagules produced by those I_{BA} infections that enter treated classes. The expected number of propagules produced in an I_{BA} class, is the rate of A propagule production $\kappa_{BA,A}$ multiplied by the expected lifetime of a I_{BA} infection ($\frac{1}{\mu_{BA}+\nu}$). The probability of transitioning to a treated class is $\frac{\nu}{\mu_{BA}+\nu}$, and the number of propagules produced while in that class is $\kappa_{TBA,A}$ multiplied by the expected lifetime of a I_{TBA} class $\frac{1}{\mu_{TBA}}$. Therefore:

$$\begin{aligned} B_C &= \sigma \frac{b}{u}\left(\frac{\kappa_{BA,A}}{\mu_{BA}+\nu} + \frac{\nu}{(\mu_{BA}+\nu)}\frac{\kappa_{TBA,A}}{\mu_{TBA}}\right) \\ &= \frac{\sigma\beta_{\mathrm{BA},A}}{\nu+\mu_{\mathrm{BA}}} + \frac{\nu\sigma\beta_{\mathrm{TBA},A}}{(\nu+\mu_{\mathrm{BA}})\,\mu_{\mathrm{TBA}}} \end{aligned}$$

We can derive B_S in precisely the same manner, we just have to keep in mind that in addition to becoming treated, an I_A class can also become infected by B. Recall that the rate of becoming doubly infected, per singly infected class, is σh_B. Therefore the expected amount of time spent in an I_A class is $\frac{1}{\nu+\sigma\hat{h}_b+\mu_A}$, and the probability of transitioning to an AB class from an A class is $\frac{\sigma\hat{h}_B}{\nu+\sigma\hat{h}_B+\mu_A}$, and hence the probability of transitioning to an I_A class to an I_{AB} class to a TAB class is $\left(\frac{\sigma\hat{h}_B}{\nu+\sigma\hat{h}_B+\mu_A}\right)\left(\frac{\nu}{\nu+\mu_{AB}}\right)$. In a similar fashion we can then write our expression for B_S.

$$\begin{aligned} B_S = &\frac{\beta_A}{\nu+\sigma\hat{h}_B+\mu_A} + \frac{\sigma\hat{h}_B\beta_{\mathrm{AB},A}}{(\nu+\mu_{\mathrm{AB}})\left(\nu+\sigma\hat{h}_B+\mu_A\right)} + \frac{\nu\beta_{\mathrm{TA},A}}{\mu_{\mathrm{TA}}\left(\nu+\sigma\hat{h}_B+\mu_A\right)} \\ &+ \frac{\nu\sigma\hat{h}_B\beta_{\mathrm{TAB},A}}{(\nu+\mu_{\mathrm{AB}})\,\mu_{\mathrm{TAB}}\left(\nu+\sigma\hat{h}_B+\mu_A\right)} \end{aligned} \tag{2.12}$$

Combining expressions, we obtain our expression for R_C,

(2.13)

$$R_C = \frac{\sigma \hat{I}_B \beta_{\mathrm{BA},A}}{\nu + \mu_{\mathrm{BA}}} + \frac{\hat{S}\beta_A}{\nu + \sigma h_B + \mu_A} + \frac{\hat{S}\sigma \hat{h}_B \beta_{\mathrm{AB},A}}{(\nu + \mu_{\mathrm{AB}})\left(\nu + \sigma \hat{h}_B + \mu_A\right)} + \frac{\hat{S}\nu\beta_{\mathrm{TA},A}}{\mu_{\mathrm{TA}}\left(\nu + \sigma \hat{h}_B + \mu_A\right)}$$
$$+ \frac{\hat{S}\nu\sigma \hat{h}_B \beta_{\mathrm{TAB},A}}{(\nu + \mu_{\mathrm{AB}})\,\mu_{\mathrm{TAB}}\left(\nu + \sigma \hat{h}_B + \mu_A\right)} + \frac{\nu\sigma \hat{I}_B \beta_{\mathrm{TBA},A}}{(\nu + \mu_{\mathrm{BA}})\,\mu_{\mathrm{TBA}}}$$

We note, that although we think about things in terms of propagule production to derive R_0 heuristically, it is not required for our biological model. Indeed, any biologically relevant explanation of the transmission efficiencies in 2.4 will result in precisely the same R_0, as we have shown in Appendix A by applying the Next Generation Theorem. Indeed, thinking of things at the level of the propagule is a prop, that allows a heuristic biologically intuitive derivation of R_0.

Now that we have derived an expression for our invasion condition, our problem of stability has been reduced to analysing R_0, where $\hat{S}$, $\hat{I}_B$ $\hat{h}_B$ denote the values of S, I_B and h_B at the endemic equilibrium. If $R_0 > 1$ then the resistant strain, strain A, will be able to invade the endemic B equilibrium and if $R_0 < 1$ then the resistant strain will not be able to invade.

Recall, that in order to obtain the threshold condition for strain A invasion (equation 2.13), we had to assume that an endemic equilibrium existed and that it was stable. We note that we cannot come up with a general algebraic expression the endemic equilibrium of system 2.7. In order to solve for the endemic equilibrium we make the following simplifying, yet still biologically relevant, assumption: a class that is singly infected has the same transmission efficiency and mortality rate as a class that is coinfected (infected twice) with the same strain [2]. This leads to the following set of assumptions:

[2]Biologically this could be explained by a strain specific immune response. Upon single infection, a strain specific immune response is initiated and therefore a second inoculum, of the same strain is not able to establish itself.

Assumption II.5. *A class that is singly infected has the same transmission efficiency and mortality rate as a class that is coinfected with the same strain*

$$\begin{aligned}
\beta_{BB,B} &= \beta_{B,B} := \beta_B \\
\beta_{TBB,B} &= \beta_{TB,B} := \beta_{TB} \\
\beta_{TAA,A} &= \beta_{TA,A} := \beta_{TA} \\
\beta_{AA,A} &= \beta_{A,A} := \beta_A \\
\mu_{TAA} &:= \mu_{TA} \\
\mu_{AA} &:= \mu_A \\
\mu_{TBB} &:= \mu_{TB} \\
\mu_{BB} &:= \mu_B,
\end{aligned}$$

where we have simplified the notation even further by allowing β_B to denote $\beta_{B,B}$ and β_A to denote $\beta_{A,A}$. Applying II.5 we can now solve for the endemic equilibrium

$$\begin{aligned}
\hat{S} &= \frac{(\nu+\mu_B)\,\mu_{\mathrm{TB}}}{\nu\beta_{\mathrm{TB}}+\beta_B\mu_{\mathrm{TB}}} \\
\hat{I}_B &= \frac{(\nu+\mu_B)\,\mu_{\mathrm{TB}} * (h_B)}{(\nu\beta_{\mathrm{TB}}+\beta_B\mu_{\mathrm{TB}})\,(\sigma h_B+(\nu+\mu_B))} \\
\hat{h}_B &= \Theta\left(\frac{\nu\beta_{\mathrm{TB}}}{(\nu+\mu_B)\,(\mu_{\mathrm{TB}})}+\frac{\beta_B}{(\nu+\mu_B)}\right)-\mu.
\end{aligned} \tag{2.14}$$

Equilibrium 2.14 is locally stable when $\hat{h}_B > 0$ (appendix A).

Substituting 2.14 into 2.13 we obtain the following expression for R_C.

$$R_C = \Gamma_A\frac{(\nu+\mu_A)}{(\nu+\sigma h_B+\mu_A)}+\frac{\sigma \mathrm{h}_B\Gamma_{\mathrm{AB}}}{(\nu+\sigma h_B+\mu_A)}+\frac{\sigma \mathrm{h}_B\Gamma_{\mathrm{BA}}}{(\nu+\sigma h_B+\mu_B)} \tag{2.15}$$

where we have made use of the following notational convention:

$$\Gamma_{\mathrm{X}} = \frac{\left(\beta_{\mathrm{X,A}}\mu_{\mathrm{TX}} + \nu\beta_{\mathrm{TX,A}}\right)}{\left(\nu + \mu_{\mathrm{X}}\right)\mu_{\mathrm{TX}}} \Big/ \frac{\left(\nu\beta_{\mathrm{TB,B}} + \beta_{B,B}\mu_{\mathrm{TB}}\right)}{\left(\nu + \mu_{B}\right)\mu_{\mathrm{TB}}} \tag{2.16}$$

Notice that if the efficiency of double infections is zero (ie $\sigma = 0$) then R_C reduces to

$$R_C = \Gamma_A$$

which is precisely the R_0 of an invading strain when only single infections are permitted, R_S, (Appendix B).

To simplify the subsequent analysis further we will also assume that order of infection does not affect the transmission efficiency or mortality rate.[3] This leads to the additional set of assumptions:

Assumption II.6. *Order of infection does not effect transmission efficiency or mortality rate*

$$\begin{aligned} \beta_{AB,A} &= \beta_{BA,A} \\ \mu_{AB} &= \mu_{BA} \end{aligned}$$

Making use of assumption II.6, R_C can now be expressed as

$$R_C = \Gamma_A \left(\frac{\nu + \mu_A}{\nu + \sigma\hat{h}_B + \mu_A} + \frac{\Gamma_{\mathrm{AB}}}{\Gamma_A} \left(\frac{\sigma\hat{h}_B}{\nu + \sigma\hat{h}_B + \mu_A} \right) \left(1 + \frac{\nu + \sigma\hat{h}_B + \mu_A}{\nu + \sigma\hat{h}_B + \mu_B} \right) \right) \tag{2.17}$$

[3] See [1] for an analysis on virulence evolution in multiple infections where this assumption has been relaxed.

CHAPTER III

The Effect of Coinfection

In this chapter we wish to establish how coinfection will affect the invasion of a resistant pathogen. To begin, with the goal of linking the within-host biology to the between-host epidemiological parameters, we will establish a general within-host model. Then assuming that resistance comes at some cost, we will consider 5 broad categories of resistance cost and establish whether coinfection increases or decreases the R_0 value under these costs of resistance. Additionaly, we will estimate the intrinsic rate of growth, r_C, when the coinfection efficiency σ is assumed to be small. We will then establish whether coinfection increases or decreases the intrinsic growth rate, when sigma is assumed to be small, for the 5 cost of resistance cases.

3.1 Linking Dynamics and the Within-Host Model

Recall that we have shown that the invasion condition for a resistant A strain under coinfection is simply $R_C > 1$. We are now interested in determining under what biological conditions coinfection will increase or decrease the R_0 value of an invading resistant mutant. In order to determine this we must come up with some way of linking what is happening biologically within individual hosts (pathogens occupying hosts, producing propagules, doing harm to their hosts, being subjected to treatment and sometimes competing with other pathogens) to what is happening

in terms of disease spread within the population. This involves linking these within host processes to quantities like $\beta_{X,Y}$, $\beta_{TX,Y}$, $\mu_{X,Y}$ ect.

One approach to linking the behaviour of these parameters to the within-host biology would be to construct an explicit time-dependent within-host model that describes the pathogen density, and in turn links the within-host dynamics to the between host epidemiological parameters. This type of model would require us to be very explicit regarding the particular within-host interactions, and since it is time-dependent it would also require us to track the infection age structure. To make such a complex model tractable we would have to make many simplifying assumptions regarding the time scale and equilibrium dynamics. In a sense, we will have accomplished all that could be accomplished with a more general cruder model but in a very roundabout and labour intensive manner [1].

With this in mind, we will begin by laying out a very general framework, for linking the interactions on a within-host level to those interactions on a between-host level. In particular, we will construct a general model, that allows us to establish relationships between the single infection epidemiological parameters (β_A, β_B, μ_A, μ_B, β_{TA}, β_{TB}, μ_{TA}, μ_{TB}) and the coinfection parameters ($\beta_{AB,A}$, $\beta_{TAB,A}$, μ_{AB}, μ_{TAB}).

Let us assume that the host contains a fixed number of sites, N. If a host is infected, individual pathogens will occupy these sites. We will assume that only one pathogen can occupy one site at a time. Now, in the absence of a different strain, a pathogen's ability to occupy sites will depend on its ability to grow. If it is "good" at growing it will be able to occupy all the sites and if it is a "poor" grower it will only occupy some fraction of the sites. Now if two different strains of pathogens are occupying a host,(eg. strain A and strain B), we must determine the fraction of the

[1] see [11] for an interesting review on nested within-host models

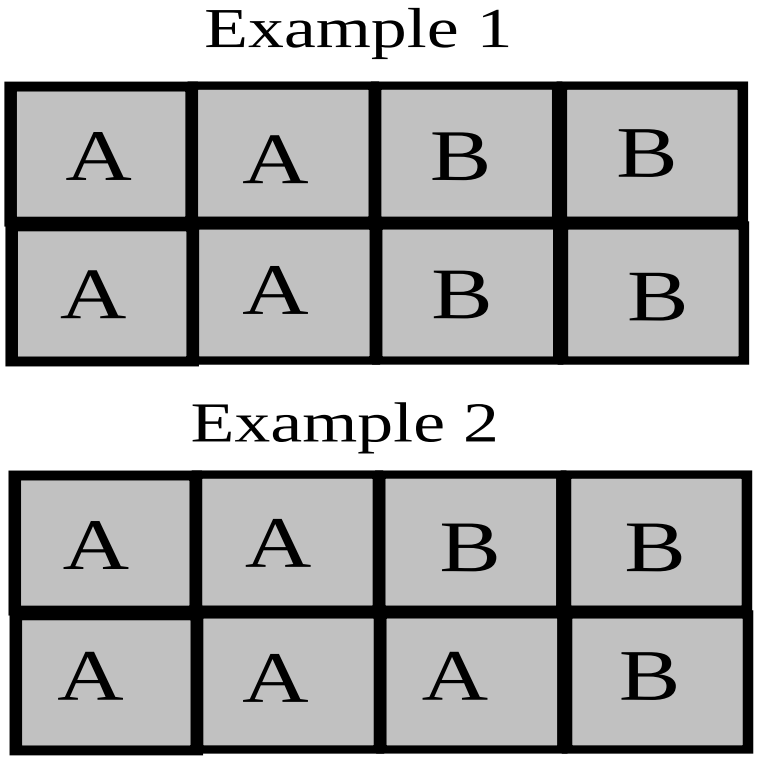

Figure 3.1: Within-host competition model. Host 1,top, A and B are equal competitors therefore they occupy an equal number of cells within a host. Host 2, bottom, A is a better, within-host, competitor than B, therefore A occupies more cells than B.

total number of sites each is able to occupy. We will assume that under coinfection, all N cells are occupied by a pathogen. We will also assume that if strain A and strain B are equal within-host competitors then they will each get an equal number of sites, $N/2$. If A is a better, within-host, competitor than B then A will be able to occupy $C > N/2$ of the sites and then of course strain B will occupy $N - C < N/2$ of the sites , and vice versa (Figure 3.1). We note that this process is assumed to be entirely independent of which strain infected the host first, and the two strains are assumed to equilibriate to their new respective densities instantaneously upon coinfection.

Now recall that we are interested in the emergence of strain A, where strain A is assumed to be resistant and strain B is assumed to be sensitive. We will assume that

drug treatment is "curative", meaning that the drug sensitive B strain is entirely wiped out upon entering a treated class and that the A strain is entirely resistant meaning that its growth is unhindered when entering a treated class. Specifically in the single infection case, we assume that if a host is infected with strain B only, upon entering a treated class the pathogen will be cleared from the host. In the single infection case, if a host is infected with strain A only, we assume that the number of sites it occupies remains constant upon entering a treated class.

In coinfection, the situation is slightly more complicated, since if strain B is wiped out due to treatment, the A strain will no longer have to compete with the B strain in the treated class. Therefore we will assume that the within-host dynamics are sufficiently fast enough so that upon entering the treated class the host behaves as if it never contained any strain B, (A is able to occupy as many sites as if it had never been coinfected). This means that, from a between host perspective, treatment and host recovery are instantaneous.

Now that we have established a general within host model, we would like to establish a link between what is happening on the within host level, and the between-host epidemiological parameters, ($\beta_{X,Y}$ and μ_X). In order to do this, we will make the general assumption that transmission efficiency [2]. and mortality are increasing functions of pathogen density. Let us denote the pathogen density of strain A and strain B respectively as, ρ_A and ρ_B then:

[2]This is what we would expect if we assumed that transmission efficiency was linked to the ability of a pathogen to consume resources.

$$
\begin{aligned}
\beta_A &= q_A F[\rho_A] \\
\beta_B &= q_B F[\rho_B] \\
\mu_A &= s_A G[\rho_A] \\
\mu_B &= s_B G[\rho_B]
\end{aligned} \tag{3.1}
$$

where F and G are increasing functions of pathogen density, and we assume that $F(0) = 0$ and $G(0) = \mu$ and q_A, q_B, s_A and s_B are scaling constants independent of pathogen density. For example, recall our expression for transmission efficiency that explicitly incorporates the propagule pathway:

$$\beta_{X,Y} = \frac{b}{u}\kappa_{X,Y}. \tag{3.2}$$

Here, for example, the expected lifetime of a propagule $\frac{1}{u}$ could be dependent on the type of propagule (A, or B), but will be independent of the pathogen density.

For the coinfection classes we assume that all N-sites are occupied, and that the transmission efficiency and the contribution of each strain to the mortality rate will depend on the total number of sites occcupied [3].

$$
\begin{aligned}
\beta_{\mathrm{AB},A} &= q_A \phi F[N] \\
\beta_{\mathrm{AB},B} &= q_B (1-\phi) F[N] \\
\mu_{\mathrm{AB}} &= \phi s_A G[N] + s_B(1-\phi)G[N],
\end{aligned}
$$

where $0 < \phi < 1$, which we will refer to as the "competition" parameter. When $\phi = 1/2$ strain A and B are equal competitors. When $\phi > 1/2$ A is considered

[3]Note, that we do not assume these type of dynamics when the second inoculum consists of the same strain.

a better within-host competitor than strain B and when $\phi < 1/2$ B is a better within-host competitor than strain A.

Therefore specifically for treated classes we will have the following relationships for the epidemiological parameters:

$$\begin{aligned}
\beta_{TB} &= 0 \\
\beta_{TA} &= \beta_A \\
\beta_{\mathrm{TAB},A} &= \beta_A \\
\beta_{\mathrm{TAB},B} &= 0 \\
\mu_{TA} &= \mu_A \\
\mu_{TB} &= \mu \\
\mu_{\mathrm{TAB}} &= \mu_A
\end{aligned}$$

3.2 Cost of Resistance

Now, typically it is assumed that resistance comes at some fitness cost to the pathogen. There are many possible pathways in which a pathogen can experience a fitness cost. We will examine the following 5 broad categories of resistance costs.

1. No Cost of Resistance
2. Reduced Transmission
3. Reduced Competition
4. Increased Mortality
5. Reduced Growth

For the no cost of resistance scenario we assume that strain A and strain B are identical, specifically that $\phi = \frac{1}{2}$, $s_A = s_B$ and that $q_A = q_B$, except that strain A is resistant to drug treatment as given by the equations in 3.3. We assume that since strain A and strain B experience no cost of resistance that they are both able to maximally occupy a host when singly infecting a host. Mathematically this can be expressed as:

$$\begin{aligned} \beta_{\mathrm{A},A} &= \beta_{B,B} \\ \beta_{\mathrm{AB},B} &= \frac{1}{2}\beta_{B,B} \\ \beta_{\mathrm{AB},A} &= \frac{1}{2}\beta_{A,A} \\ \mu_A &= \mu_B \\ \mu_{\mathrm{AB}} &= \frac{\mu_A + \mu_B}{2} = \mu_A \end{aligned} \tag{3.3}$$

For the reduced transmission cost we assume that the transmission parameter of strain A is less than the transmission parameter of strain B. The competition parameter remains unaffected as well as the mortality effects. This is analogous to the assumption that strain B is able to compete as well as strain A, within the host, but is unable to transmit as well between hosts. In other words in a single infection case, both strain A and strain B occupy all N sites of a host, but we assume that $q_A < q_B$, but $s_A = s_B$. In terms of the epidemiological parameters this can be expressed as:

$$
\begin{aligned}
\beta_{\mathrm{A},A} &< \beta_{B,B} \\
\beta_{\mathrm{AB},B} &= 1/2\beta_{B,B} \\
\beta_{\mathrm{AB},A} &= 1/2\beta_{A,A} \\
\mu_A &= \mu_B \\
\mu_{\mathrm{AB}} &= \frac{\mu_A + \mu_B}{2} = \mu_A
\end{aligned} \tag{3.4}
$$

For the reduced competition cost we assume that strain A cannot compete as well as strain B within the host, but otherwise there is no cost of resistance. In other words, when there is no coinfection strain A behaves identically to strain B. Therefore, both strain A and B are able to occupy all N sites when singly occupying a host and $q_A = q_B$ and $s_A = s_B$, however $\phi < \frac{1}{2}$. In terms of the epidemiological parameters this can be expressed as:

$$
\begin{aligned}
\beta_{\mathrm{A},A} &= \beta_{B,B} \\
\beta_{\mathrm{AB},B} &= (1-\phi)\,\beta_{B,B} \\
\beta_{\mathrm{AB},A} &= \phi\beta_{A,A} \\
\mu_A &= \mu_B \\
\mu_{\mathrm{AB}} &= \phi\mu_A + (1-\phi)\mu_B = \mu_A
\end{aligned} \tag{3.5}
$$

where $\phi < 1/2$.

For the increased mortality cost we assume that, in the single infection case both strains are able to occupy all N sites of the host. We also assume that within-host competition is unaffected, $\phi = \frac{1}{2}$, as well as the transmission parameters, $q_A = q_B$,

but that strain A contributes to within-host mortality more than strain B, $s_A > s_B$. In terms of the epidemiological parameters this can be expressed as:

$$\begin{aligned} \beta_{\mathrm{A},A} &= \beta_{B,B} \\ \beta_{\mathrm{AB},B} &= 1/2\beta_{B,B} \\ \beta_{\mathrm{AB},A} &= 1/2\beta_{A,A} \\ \mu_A &> \mu_B \\ \mu_{\mathrm{AB}} &= \frac{\mu_A + \mu_B}{2} \end{aligned} \tag{3.6}$$

In the reduced growth scenario,we assume that strain A does not grow as well as strain B within the host. This means that in the single infection case the B strain is assumed to occupy all of the N sites, but the A strain is assumed to occupy less than N sites. However we assume that $q_B = q_A$, and $s_A = s_B$. In the coinfection case, we assume that this reduced growth rate translates to a reduced competitive ability $\phi < \frac{1}{2}$. In terms of the epidemiological parameters this can be expressed as:

$$\begin{aligned} \beta_{\mathrm{A},A} &< \beta_{B,B} \\ \beta_{\mathrm{AB},B} &= (1-\phi)\,\beta_{B,B} \\ \beta_{\mathrm{AB},A} &= \phi\beta_{B,B} \\ \mu_A &< \mu_B \\ \mu_{\mathrm{AB}} &= \phi\mu_B + (1-\phi)\mu_B = \mu_B \end{aligned} \tag{3.7}$$

We summarize these cases in table 3.1.

Table 3.1: Cost of Resistance Parameter Assumptions

Cost of Resistance	Conditions				
No Cost (NC)	$\beta_{\mathrm{A},A} = \beta_{B,B}$	$\beta_{\mathrm{AB},B} = \frac{1}{2}\beta_{B,B}$	$\beta_{\mathrm{AB},A} = \frac{1}{2}\beta_{A,A}$	$\mu_A = \mu_B$	$\mu_{\mathrm{AB}} = \mu_B$
Reduced Transmission (RT)	$\beta_{\mathrm{A},A} < \beta_{B,B}$	$\beta_{\mathrm{AB},B} = \frac{1}{2}\beta_{B,B}$	$\beta_{\mathrm{AB},A} = \frac{1}{2}\beta_{A,A}$	$\mu_A = \mu_B$	$\mu_{\mathrm{AB}} = \mu_B$
Poor Competitor (PC)	$\beta_{\mathrm{A},A} = \beta_{B,B}$	$\beta_{\mathrm{AB},B} = (1-\phi)\,\beta_{B,B}$	$\beta_{\mathrm{AB},A} = \phi\beta_{A,A}$, $\phi < \frac{1}{2}$	$\mu_A = \mu_B$	$\mu_{\mathrm{AB}} = \mu_B$
Reduced Growth (RG)	$\beta_{\mathrm{A},A} < \beta_{B,B}$	$\beta_{\mathrm{AB},B} = (1-\phi)\,\beta_{B,B}$	$\beta_{\mathrm{AB},A} = \phi\beta_{B,B}$, $\phi < \frac{1}{2}$	$\mu_A < \mu_B$	$\mu_{\mathrm{AB}} = \mu_B$
Increased Mortality (IM)	$\beta_{\mathrm{A},A} = \beta_{B,B}$	$\beta_{\mathrm{AB},B} = \frac{1}{2}\beta_{B,B}$	$\beta_{\mathrm{AB},A} = \frac{1}{2}\beta_{A,A}$	$\mu_A > \mu_B$	$\mu_{\mathrm{AB}} = \frac{\mu_A+\mu_B}{2}$

3.3 The Effect of Coinfection on R_0

Now recall that previously we have obtained a threshold condition for the invasion of a resistant pathogen A. We are interested in looking at how the presence of coinfection effects the emergence of resistance. Worded another way, we ask "how is the R_0 of a resistant strain affected by coinfection?. To elucidate how coinfection effects the R_0 value we rewrite equation 2.17 in the following form:

$$R_C = R_S\left(w + (1-w)g\right), \tag{3.8}$$

where:

$$w = \frac{(\nu + \mu_A)}{\left(\nu + \mu_A + \sigma\hat{h}_B\right)} \tag{3.9}$$

and

$$g = fk \tag{3.10}$$

where

$$f = (\Gamma_{\mathrm{AB}}/\Gamma_A) \tag{3.11}$$

and

$$k = \left(1 + \frac{\nu + \sigma\ \hat{h}_B + \mu_A}{\left(\nu + \sigma\hat{h}_B + \mu_B\right)}\right). \tag{3.12}$$

From equation 3.8 we can see that to determine if allowing for coinfection, as opposed to single infections only, increases or decreases the value of R_0, it suffices to look at the behaviour of

$$g = fk = (\Gamma_{\mathrm{AB}}/\Gamma_A)\left(1 + \frac{\nu + \sigma\ \hat{h}_B + \mu_A}{\left(\nu + \sigma\hat{h}_B + \mu_B\right)}\right)$$

compared to 1. If $g > 1$ then coinfection increases the R_0 value of a resistant strain, if $g < 1$ then coinfection decreases the R_0 of a resistant strain if $g = 1$ then coinfection has no effect on the resistant strain.

In order to gain a more intuitive understanding of why the effect of coinfection on R_0 should depend only on the magnitude of g relative to 1 we offer a biological explanation of the terms contained in g.

Let us begin by examining the quantity $f = (\Gamma_{\mathrm{AB}}/\Gamma_A)$. Note that we can rearrange f into the following form:

$$\frac{\frac{\beta_{\mathrm{AB},A}}{(\nu+\mu_{\mathrm{AB}})} + \frac{\nu\beta_{\mathrm{TAB},A}}{(\nu+\mu_{\mathrm{AB}})(\mu_{\mathrm{TAB}})}}{\frac{\beta_{A,A}\mu_{\mathrm{TA}}}{(\nu+\mu_A)} + \frac{\nu\beta_{\mathrm{TA},A}}{(\nu+\mu_A)(\mu_{\mathrm{TA}})}} \tag{3.13}$$

We notice that the denominator is the transmission factor, the number of expected propagules produced per host, in a single infection case and the numerator is the transmission factor for a coinfected case. Writing expression 3.13 in terms of propagules we get:

$$\frac{\frac{b}{u}\left(\frac{\kappa_{\mathrm{AB},A}}{(\nu+\mu_{\mathrm{AB}})} + \frac{\nu\kappa_{\mathrm{TAB},A}}{(\nu+\mu_{\mathrm{AB}})(\mu_{\mathrm{TAB}})}\right)}{\frac{b}{u}\left(\frac{\kappa_A\mu_{\mathrm{TA}}}{(\nu+\mu_A)} + \frac{\kappa\beta_{\mathrm{TA}}}{(\nu+\mu_A)(\mu_{\mathrm{TA}})}\right)} \tag{3.14}$$

Since we can factor out $\frac{b}{u}$ we see that we can identify f as the total number of A propagules produced by coinfected class versus the total number of A propagules produced by an A strain in the single infection case.

Now let us examine expression 3.12. If we do not substitute the expressions for the endemic equilibrium, we can rewrite k in the following form:

$$k = 1 + \frac{\hat{I}_B \sigma}{\hat{S}} \frac{\nu + \sigma \hat{h}_B + \mu_a}{\sigma \hat{h}_B} \tag{3.15}$$

For illustration sake let us assume that $f = \frac{1}{2}$; in other words, an AB class will produce half as many new A infections as an A class, in the single infection case.

Now for coinfection to increase the R_0 value, we must have that $g > 1$ therefore $k > 2$. Alternatively:

$$\sigma \hat{I}_B > \frac{\hat{S} \sigma \hat{h}_B}{\nu + \sigma \hat{h}_B + \mu_A}. \tag{3.16}$$

Multiplying both sides by $\frac{b}{u}$ we have

$$\frac{b}{u} \sigma \hat{I}_B > \frac{b}{u} \frac{\hat{S} \sigma \hat{h}_B}{\nu + \sigma \hat{h}_B + \mu_A}. \tag{3.17}$$

In this form it is clear that we can interpret the left-hand side as the expected number of I_{BA} infections, $\mathbb{E}[I_{BA}]$, produced by an invading A propagule and the right-hand side can be interpreted as the expected number of I_{AB} infections, $\mathbb{E}[I_{BA}]$, produced by an invading A propagule. Therefore if $f = \frac{1}{2}$ then for coinfection to increase the R_0 value of A there must be more I_{BA} infections produced then I_{AB} infections. k is therefore a measure of the number of I_{BA} infections produced relative to the number of I_{AB} infections.

Therefore we can view whether or not coinfection increases the R_0 value as the result of how much production an A strain gets out of a coinfection class, as well as how many additional "susceptibles", (ie. singly infected classes) it gets as a result of

coinfection, the number of I_{BA}'s formed, relative to the number of new "susceptibles" a B strain will get as a result of coinfection, the number of I_{AB}'s formed.

3.3.1 The Effect of Coinfection on R_0 when Resistance Pays a Cost

Recall that we are interested in how treatment effects the emergence of a resistant pathogen in a coinfection scenario versus a single infection scenario. We assume that treatment is completely "curative", ($\beta_{TB} = 0$, $\mu_{TB} = \mu$, $\beta_{TAB} = \beta_A$, $\mu_{TAB} = \mu_A$) and that strain A pays some fitness cost associated with its resistance. We will compare the behaviour of R_0 in a coinfection scenario, R_C, versus R_0 in a single infection scenario, R_S for the various cost of resistance cases outlined in section 3.2.

Let us begin by assuming the simplest scenario, that the A strain pays no cost for its resistance. Recall the general form of f:

$$f = \frac{\frac{\beta_{\mathrm{AB},A}}{(\nu+\mu_{\mathrm{AB}})} + \frac{\nu\beta_{\mathrm{TAB},A}}{(\nu+\mu_{\mathrm{AB}})(\mu_{\mathrm{TAB}})}}{\frac{\beta_{A,A}\mu_{\mathrm{TA}}}{(\nu+\mu_A)} + \frac{\nu\beta_{\mathrm{TA},A}}{(\nu+\mu_A)(\mu_{\mathrm{TA}})}}.$$

Now since we have assumed that the A strain is completely resistant, $\mu_{TA} = \mu_A$ and $\beta_{TA} = \beta_A$. We can rewrite the denominator to obtain

$$f = \frac{\frac{\beta_{\mathrm{AB},A}}{(\nu+\mu_{\mathrm{AB}})} + \frac{\nu\beta_{\mathrm{TAB},A}}{(\nu+\mu_{\mathrm{AB}})(\mu_{\mathrm{TAB}})}}{\frac{\beta_A}{\mu_A}}.$$

It is clear that since treatment has no effect on strain A, the dominator is equivalent to the transmission factor, (expected number of propagules produced per susceptible), of an A strain when only single infections are permitted and there is no treatment. We also note that $\frac{\beta_A}{\mu}\frac{u}{b}$ can be interpreted as the total number of A propagules produced by an I_A class in the single infection case. Recall from equation 3.14 that we can get the $\frac{b}{u}$ to cancel so that we can interpret the terms in terms of propagule production. We also note that we can view the numerator of f as a contribution from

two different classes. The quantity $\frac{\beta_A}{\nu+\mu_{AB}}\frac{u}{b}$ is the number of propagules produced by a coinfection class when there is no treatment, whereas $\frac{\nu\beta_{\mathrm{TAB},A}}{(\nu+\mu_{\mathrm{AB}})(\mu_{\mathrm{TAB}})}\frac{u}{b}$ is the additional number of propagules produced by a coinfected class as a result of treatment. This interpretation of the terms of f, will aid us in understanding the effect on f for different costs of resistance.

Now applying assumptions 3.3, we obtain the following expression for f in the no cost of resistance case:

$$\begin{aligned} f &= (\Gamma_{\mathrm{AB}}/\Gamma_A) \\ &= \frac{(\beta_{\mathrm{AB},A}\mu_{\mathrm{TAB}} + \nu\beta_{\mathrm{TAB},A})\,(\nu+\mu_A)\,(\mu_{\mathrm{TA}})}{(\nu+\mu_{\mathrm{AB}})\,(\mu_{\mathrm{TAB}})\,(\beta_A\mu_{\mathrm{TA}} + \nu\beta_{\mathrm{TA}})} \\ &= \frac{(1/2\mu_A+\nu)}{(\nu+\mu_A)} > 1/2. \end{aligned}$$

Examining our expression for f we notice that if there was no treatment, ($\nu = 0$), a coinfected class, (AB or BA), is expected to produce half as many propagules as an A class; i.e. $f = \frac{1}{2}$. However, since $\nu > 0$, some fraction of AB and BA infections will become treated. Recall that we have assumed that the B strain is entirely treatment sensitive and that the A strain is entirely resistant, and is able to recover to single infection densities when it no longer has to compete with strain B. Therefore, those coinfected classes, AB or BA, that become treated effectively produce propagules as if they were I_A classes only. As a result since $\nu > 0$, we have that $f > 1/2$. We also note that f will increase as the amount of treatment increases.

Now examining k we have:

$$\begin{aligned} k &= \left(1 + \frac{\nu + \sigma\ \hat{h}_B[\nu] + \mu_A}{\nu + \sigma\hat{h}_B[\nu] + \mu_B}\right) \\ &= 2. \end{aligned}$$

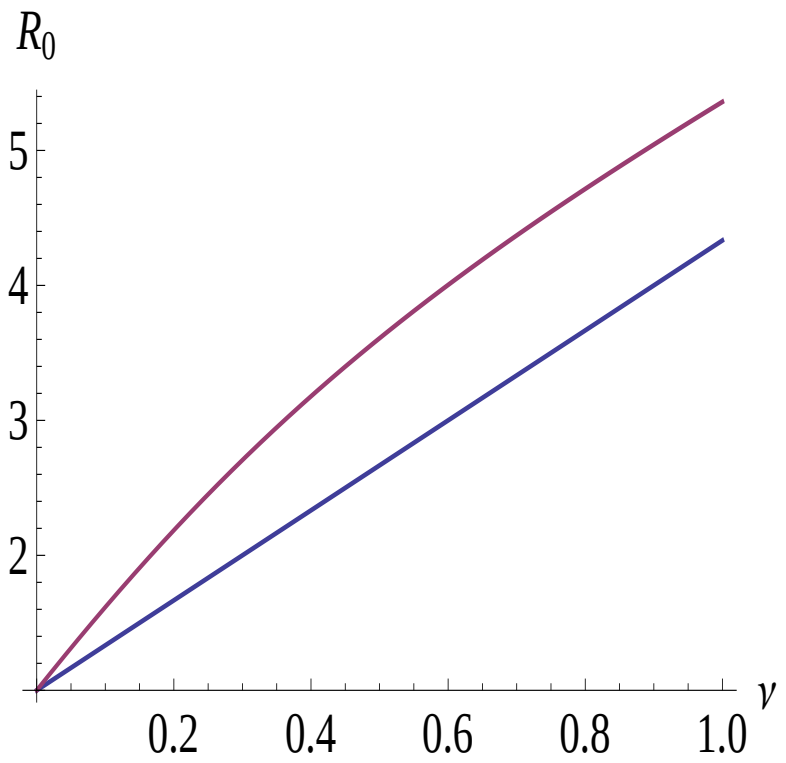

Figure 3.2: R_0 vs. treatment rate, ν, for coinfection and single infection case when there is no cost of resistance. Red Line: R_0 for the coinfection case, Blue line: R_0 for the single infection case, $\Theta = 0.1$, $\beta_B = 0.08$, $\mu_B = 0.02$, $\mu_A = 0.02$, $\sigma = 0.8$. All units in day^{-1}

In other words, we expect there to be as many I_{BA} infections produced as I_{AB} infections. Hence, $g > 1$ and coinfection will increase the R_0 value of the A strain when there is treatment.

Figure 3.2 depicts R_C and R_S as a function of treatment rate, ν, for the no cost of resistance case. We see that when there is no treatment (i.e. $\nu = 0$) $R_C = R_S = 1$. Since, we have assumed that there is no cost of resistance, when $\nu = 0$, the two strains are indistinguishable and therefore both R_C and R_S will be equal to one. When $\nu > 0$, $R_C > R_S$, because the A strain will be able to completely monopolize those coinfected hosts which become treated.

In a similar fashion we can apply 3.3 and assumptions 3.4, 3.5, 3.6, 3.7 for the reduced transmission, reduced competition, increased mortality and reduced growth

cases respectively. Table 3.2 summarizes the f and k values for the various cost of resistance cases when there is treatment, ($\nu > 0$). Figure 3.3 gives example plots of R_C and R_S versus ν for the reduced transmission, reduced growth, poor competitor and increased mortality cost of resistance cases.

Table 3.2: Effect of Coinfection on R_0 with treatment ($\nu > 0$)

	R_S	f	k	g, ($\nu > 0$)	R_C
NC	$\frac{(\nu+\mu_b)}{(\mu_b)}$	$\frac{(1/2\mu a+\nu)}{(\nu+\mu a)}$	2	> 1	$R_C > R_S$
RT	$\frac{(\beta_A)(\nu+\mu_B)}{(\beta_B)(\mu_B)}$	$\frac{(1/2\mu_B+\nu)}{(\nu+\mu_B)}$	2	> 1	$R_C > R_S$
RG	$\frac{(\beta_A)(\nu+\mu_B)}{(\beta_B)(\mu_A)}$	$\frac{\left(\phi\frac{\beta_B}{\beta_A}\mu_A+\nu\right)}{(\nu+\mu_B)}$	$\left(1+\frac{\nu+\sigma\hat{h}_B[\nu]+\mu_A}{\nu+\sigma\hat{h}_B[\nu]+\mu_B}\right)$	$g = 1$ or < 1 or > 1	Indeterminate
PC	$\frac{(\nu+\mu_B)}{(\mu_B)}$	$\frac{(\phi\mu_A+\nu)}{(\mu_A+\nu)}$	2	$g = 1$ or > 1 or < 1	Indeterminate
IM	$\frac{(\nu+\mu_B)}{(\mu_A)}$	$\frac{(1/2\mu_A+\nu)}{(\nu+1/2\mu_A+1/2\mu_B)}$	$\left(1+\frac{\nu+\sigma\hat{h}_B[\nu]+\mu_A}{\nu+\sigma\hat{h}_B[\nu]+\mu_B}\right)$	$g > 1$	$R_C > R_S$

When the cost of resistance is reduced transmission f and k take on identical forms as in the no cost of resistance case. This makes sense as we have only reduced the transmission efficiency of the A strain, and f is a measure of the propagule production relative to the single infection case. Therefore the $q_A s$ will cancel out. Also, we would not expect the transmission efficiency of A to effect the number of I_{BA} infections relative to the number of I_{AB} infections.

To illustrate this, recall our expressions for the expected number of I_{BA} infections, $\mathbb{E}[I_{BA}]$, and the expected number of I_{AB} infections produced, $\mathbb{E}[I_{AB}]$,(equation 3.17).

$$\mathbb{E}[I_{BA}] = \frac{b}{u}\sigma\hat{I}_B$$

$$\mathbb{E}[I_{AB}] = \frac{b}{u}\frac{\hat{S}\sigma\hat{h}_B}{\nu+\sigma\hat{h}_B+\mu_A}$$

Now, since the initial assumption is that A is rare, the strain A epidemiological

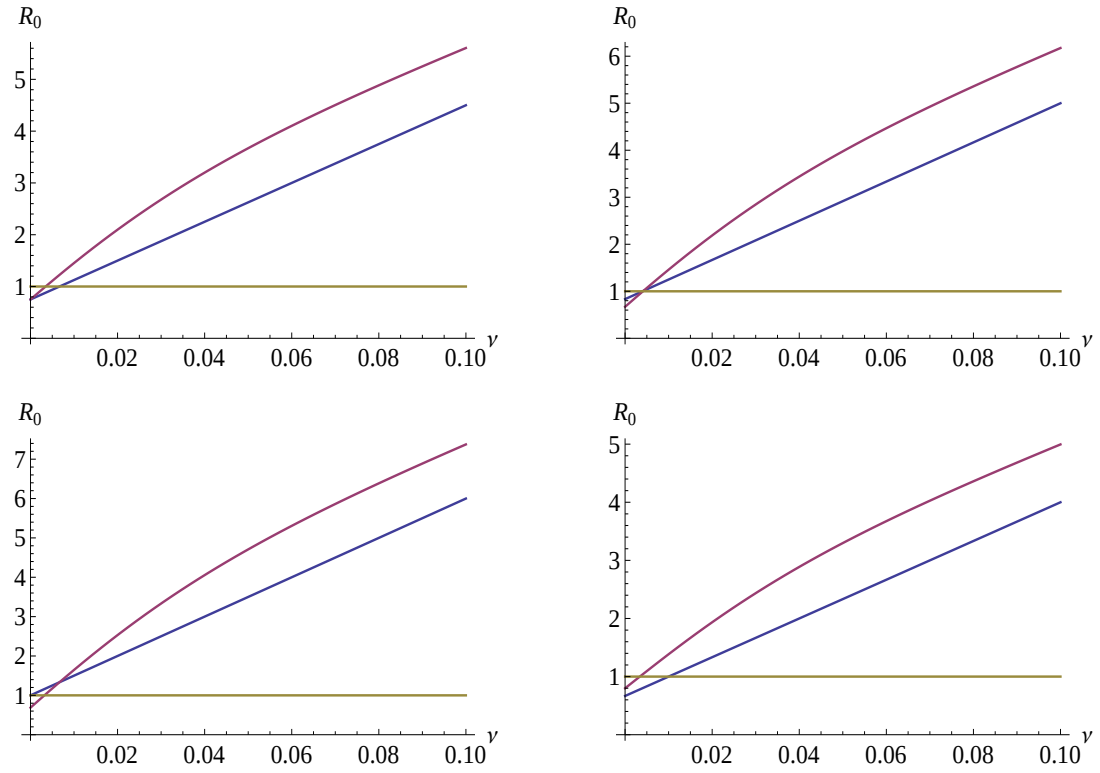

Figure 3.3: R_0 vs. treatment rate (ν) for coinfection and single infection case when resistance pays a cost. Red lines: R_0 for the Coinfection case, blue lines: R_0 for the single infection case. Top left: Cost of Resistance Reduced Transmission $\Theta = 0.1$, $\beta_B = 0.08$, $\beta_A = 0.06$, $\mu_B = 0.02$, $\mu_A = 0.02$, $\sigma = 0.8$, $\mu = 0.004$,Top Right: Cost of Resistance Reduced Growth $\Theta = 0.1$, $\beta_B = 0.08$, $\beta_A = 0.07$, $\mu_B = 0.02$, $\mu_A = 0.015$, $\sigma = 0.8$, $\mu = 0.004$, $\phi = 1/3$ Bottom Left: Cost of Resistance Poor Competitor $\Theta = 0.1$, $\beta_B = 0.08$, $\beta_A = 0.08$, $\mu_B = 0.02$, $\mu_A = 0.02$, $\sigma = 0.8$, $\mu = 0.004$, $\phi = 1/3$, Bottom Right: Increased Mortality $\Theta = 0.1$, $\beta_B = 0.08$, $\beta_A = 0.08$, $\mu_B = 0.02$, $\mu_A = 0.03$, $\sigma = 0.8$, $\mu = 0.004$, $\phi = 1/3$. ϕ is unitless, the rest of the units are in day^-1

parameters will not determine the equilibrium values of $\hat{S}$, $\hat{h}_B$ or $\hat{I}_B$. Therefore the only place where a reduction in A transmission effficiency may effect $\mathbb{E}[I_{AB}]$ or $\mathbb{E}[I_{BA}]$ is in the "b" or "μ" parameter, since β_A:

$$\beta_{A,A} = \frac{b\kappa_{A,A}}{u} \tag{3.18}$$

However f is the ratio of $\frac{\mathbb{E}[I_{BA}]}{\mathbb{E}[I_{AB}]}$ therefore $\frac{b}{\mu}$ will cancel out of f and we conclude that a reduction in A transmission will not effect the value of f. We therefore conclude that $g > 1$, when $\nu > 0$ for the reduced transmission cost of resistance. Therefore when there is treatment $R_C > R_S$. In other words coinfection will increase the R_0 value of the resistant strain.

Refering to figure 3.3 top left we see that we get a similar graph, as in the no cost of resistance case. However when $\nu = 0$, $R_C = R_S < 1$, since the reduced transmission cost of resistance makes the R_0 value without treatment less than unity. When we begin to increase treatment ($\nu > 0$), those coinfected individuals that become treated will be taken over by the A strain and produce A propagules only, making $R_C > R_S$. We note that there exists some treatment rate, $\nu*$, where $R_C > 1$ but $R_S < 1$. Therefore coinfection will cause the resistant A strain to emerge at a lower treatment rate than in the single infection only case.

For the the reduced growth cost of resistance case we have that:

$$f = \frac{\left(\phi\frac{\beta_B}{\beta_A}\mu_A + \nu\right)}{(\nu + \mu_B)}.$$

If there is not treatment, $f = \phi\frac{\beta_B\mu_A}{\beta_A\mu_B} = \phi\frac{1}{R_S}$, which will be greater than $\frac{1}{2}$ when $R_S > 1$ since $\phi < \frac{1}{2}$. However if $R_S < 1$ then f can be larger or smaller than $\frac{1}{2}$ because β_A and μ_A are affected by the reduction of growth, it is not clear what value

f will take. Similarly to the no cost case, those coinfections that become treated will increase the value of f, since those treated classes will behave as if they contained only A strains. We note that as ν becomes large, $f \to 1$. In other words when the treatment effect,(coinfected classes becoming treated and transmitting A propagules only) dominates, $f > \frac{1}{2}$. For the reduced growth cost of resistance, we have that $k < 2$. This is because we assume that, due to the reduced growth of the A strain $\mu_A < \mu_B$. Therefore on average an I_A class will exist longer than an I_B class, meaning that an I_A class will have more opportunity to become coinfected then an I_B class. In other words more I_{AB} infections will be produced relative to I_{BA} infections. This presents a disadvantage to the A strain as it will be exploited more by B strains than it will be able to exploit I_B infections. We also note that as ν becomes large compared to $\sigma\hat{h}_B$ and μ_A and μ_B, $k \to 2$. In other words for high enough treatment levels, the difference between mortality rates will become less significant because single infections are much more likely to become treated than to become coinfected. We therefore cannot determine the specific value of g relative to one. As a result, coinfection can either increase or decrease the R_0 value of strain A depending on the particular parameters. However we do note that at ν gets large then $g > 1$, and coinfection will increase the R_0 value of strain A.

Figure 3.3 top right shows R_0 as a function of ν in the single infection and coinfection case, for a specific choice of parameters. When $\nu = 0$ $R_S > R_C$ but as ν increases the order switches at some specific value of treatment, $\nu*$, and $R_C > R_S$. In this scenario, depending on the level of treatment ν, coinfection can increase or decrease the R_0 value of the resistant strain A. Notice in figure 3.3, top right, that there is a region of treatment where the resistant strain will be able to invade if single infections only are permitted but will not be able to invade in the coinfection case,

(i.e. the region of the graph where $R_C < 1$ and $R_S > 1$).

For the poor competitor cost of resistance we have that

$$f = \frac{(\phi\mu_A + \nu)}{(\mu_A + \nu)}. \tag{3.19}$$

If there is no treatment $f < \frac{1}{2}$. This makes sense, as the assumption is that A is a poor competitor compared to strain B in a coinfected class. Therefore we expect that A will produce less than half of the propagules in a coinfected class as in a single infection case. However, again as we increase treatment we have f increasing, as now some fraction of coinfected individuals will become treated and A will be able to completely monopolize those hosts. As ν gets large $f \to 1$. Therefore when there is treatment we cannot determine the value of f relative to $\frac{1}{2}$ since it will depend on the specific parameters. Since the poor competitor cost of resistance does not affect the parameters in a single infection case we have that $k = 2$. We cannot determine the magnitude of g relative to one, since it will depend on the individual parameters. Therefore we conclude that coinfection can either decrease the R_0 value or increase the R_0 value or have no effect on the R_0 value of the A strain.

Figure 3.3 bottom left, plots R_S and R_C versus ν for a given choice of parameters. We see that when $\nu = 0$, $R_S < R_C$. We then have that as ν increases to $\nu*$ the order switches and $R_C > R_S$. For this choice of parameters there is a region of the graph where $R_C > 1$ but $R_S < 1$, meaning that the presence of coinfection will allow the A strain to invade, but in the single infection case the A strain will not be able to invade.

For the increased mortality scenario we have that

$$f = \frac{(1/2\mu_A + \nu)}{(\nu + 1/2\mu_A + 1/2\mu_B)}.$$

If there was no treatment $f > \frac{1}{2}$. Now under this assumption the rate of propagule production of a coinfected class, will be exactly half of the rate of propagule production for a single infection case. However, the expected lifetime of an I_A class in the single infection case will be smaller than the expected lifetime of a coinfected class since $\mu_A > \mu_B$, and in the coinfection case we assume that μ_{AB} is an average of the mortality rate of strain A , μ_A, and the mortality rate of strain B, μ_B. Therefore the total expected production of A propagules will be greater than one half of the expected production of propagules in the single infection case, since an I_{AB} class will live longer than an I_A class, in the single infection case, and therefore will produce more propagules. Now when $\nu > 0$ we will still have that $f > \frac{1}{2}$, since those coinfected classes that become treated will produce more than twice as many A propagules as before, and as treatment increases $f \to 1$. Now examining our expression for k, we have that $k > 2$ since $\mu_A > \mu_B$. This is because an I_B class will live longer on average than an I_A class and therefore will have more opportunity to become coinfected. Therefore there will be more I_{BA} classes produced than I_{AB} classes. When ν gets large $k \to 2$ because I_A and I_B classes will become treated before they have a chance to become coinfected. Therefore we conclude that $g > 1$ and that coinfection increases the R_0 value of the A propagule.

Figure 3.3 bottom left plots R_S and R_C versus ν for the increased mortality case. We see that R_C always lies above R_S. Refering to the graph, when $\nu = 0$ both R_S and R_C are less than unity. As we increase the treatment rate, ν, we see that there is a region of the graph where R_C is greater than one but R_S is still less than one. Therefore, when coinfection is present a resistant strain will be able to emerge at a

lower treatment rate than in the single infection only case.

We have shown that the effect of coinfection depends on the cost of resistance, the amount of treatment and in some cases the particular relationships between parameters. For the no cost of resistance and reduced transmission cases coinfection increases the R_0 value of the A strain ($R_C > R_S$), for $\nu > 0$. For the reduced growth scenario, the overall effect of coinfection depends on the particular parameter choices and is therefore indeterminate. However, if the treatment rate becomes large enough coinfection will increase the R_0 value of the A strain. In the poor competitor scenario $R_S < R_C$ when there is no treatment, however as we increase treatment this effect can be reversed. Again, however, if the treatment rate becomes large enough coinfection will increase the R_0 value of the A strain. For the increased mortality cost, when there is no treatment, coinfection increases the R_0 value of the A strain and this effect is preserved as we increase treatment.

Figure 3.4 gives a pictorial representation of the effect of coinfection on the various costs of resistance when $\nu > 0$. We have also demonstrated that there exist parameter regions where coinfection results in the emergence of resistant pathogens, where in such regions the A strain would not emerge if single infections only were permitted. We have demonstrated the important factors which determine the effect of coinfection for the emergence of resistant pathogens. We have demonstrated a method for disentangling the various factors that determine the effect of coinfection, in particular f and k, the production of a coinfected class and the resistant strain's ability to takeover singly infected resident strains relative to how often it will get taken over. Certainly, we have not exhausted the various costs of resistances, or the types of constraints we can put on particular parameters for various biologically feasible scenarios. However we have introduced a general methodology that can be

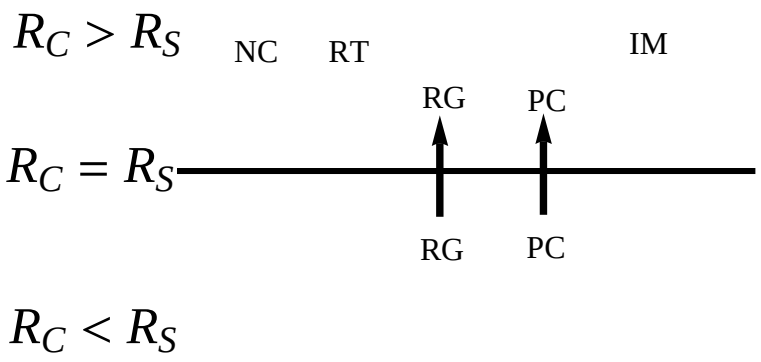

Figure 3.4: How the R_0 in a single infection case, R_S, compares to the R_0 in a coinfection case, R_C when there is treatment, ($\nu > 0$). $R_C > R_S$ In the no Cost of Resistance Case (NC), Reduced Transmission Case (RT), and Increased Mortality case (IM). For a specific set of parameters $R_C > R_S$ or $R_S > R_C$ or $R_C = R_S$ The arrows depict the trend as we increase treatment. Or in other words if ν is sufficiently large enough $R_C > R_S$ for the reduced growth and poor competitor cases.

easily expanded for more sophisticated biological scenarios. From a public health perspective, we have clearly illustrated the relevant factors, when determining the effect of coinfection on the emergence of resistant pathogens. We also note, that this increased understanding of coinfection, would be particularly advantageous in an experimental setting and could help motivate the design of experiments regarding the effect of coinfection on pathogen resistance.

3.4 The Effect of Coinfection on the Intrinsic Growth Rate when Resistance Pays a Cost

Although R_0 is a useful quantity to analyze if we are simply interested in whether or not a resistant strain will invade, or if the quantity of interest is the number of

new propagules produced by a single propagule it does not give us any information regarding the time-scale of invasion. We also note, that in general, it is not true that:

$$R_{01} > R_{02} => r_1 > r_2,$$

where R_{01} and R_{02} are two distinct R_0 values and r_1 and r_2 are their respective dominant eigenvalues. Therefore, if we are interested in how the amount of resistance changes as a function of time it may be more useful to examine the dominant eigenvalue of the Jacobian J_A. This will allows us to obtain an estimate for the fraction of resistance as a function of time. From a practical perspective this may be a more useful quantity. For example, take the case of Malaria. In this case the WHO recommends that a drug be discontinued from use when levels of resistance reach 10 percent [22]. So in the case that a resistant strain has invaded the population, how much does coinfection effect the rate of spread of resistance? Would coinfection cause a drug to reach threshold,(e.g. 10 % resistance) levels sooner, and therefore effectively reduce the life expectancy of a particular drug? Certainly these are very important and timely questions to be asking which could lead to coinfection becoming an entirely new target for disease control intervention strategies. Although we cannot obtain an algebraic expression for the dominant eigenvalue, we can estimate the dominant eigenvalue when sigma is small by using perturbation analysis.

Perturbation analysis can be used to approximate the solution of a characteristic equation when we can assume that some parameter is small and when this parameter is zero we are able to solve for the eigenvalue. One natural choice would be to examine when the probability of coinfection is low, σ is near zero. This would be a biologically relevant assumption, since for example the invasion of a pathogen can initiate an immune response, that could be general to both strains, therefore reducing

the probability of coinfection. Although, we make note that this is not necessarily always the case, for example an initial infection could potentially facilitate additional infection, $\sigma > 1$ [1].

We begin the analysis by solving for the dominant eigenvalue of system 2.4 at the endemic equilibrium when $\sigma = 0$. Recall that the Jacobian of system 2.4 can be written in the block triangular form, 2.8, and therefore the eigenvalues are just the eigenvalues of the diagonal blocks. We have shown previously that J_B is equivalent to the B only system, and that it is stable, (the real parts of all eigenvalues are less than zero), at the endemic equilibrium when $\hat{h}_B > 0$, (see Appendix A). If invasion of the A strain occurs then the dominant eigenvalue will be a solution to the characteristic equation of the the block matrix J_A. Applying assumptions II.5 and II.6 we obtain the following dominant eigenvalue for J_A, (when $\sigma = 0$)

(3.20)
$$s(J_A) = \frac{1}{2}\left(-\nu + \hat{S}\beta_A - \mu_A - \mu_{\mathrm{TA}} + \sqrt{\left(\nu - \hat{S}\beta_A + \mu_A + \mu_{\mathrm{TA}}\right)^2 - 4\left(-\hat{S}\nu\beta_{\mathrm{TA}} + \nu\mu_{\mathrm{TA}} - \hat{S}\beta_A\mu_{\mathrm{TA}} + \mu_A\mu_{\mathrm{TA}}\right)}\right).$$

Substituting in the treatment assumptions 3.3, and the particular case assumptions from Table 3.1 into 3.20 we obtain the dominant eigenvalue for each case of resistance cost when $\sigma = 0$. We denote this eigenvalue by r_S. These are summarized in Table 3.3.

Table 3.3: Dominant Eigenvalue when $\sigma = 0$ (r_S)

	Eigenvalue $\sigma = 0$ (r_S)
No Cost (NC)	ν
Reduced Transmission (RT)	$\frac{\nu\beta_A + \beta_A\mu_B - \beta_B\mu_B}{\beta_B}$
Reduced Growth(RG)	$\frac{\nu\beta_A - \beta_B\mu_A + \beta_A\mu_B}{\beta_B}$
Poor Competitor (PC)	ν
Increased Mortality (IM)	$\nu - \mu_A + \mu_B$

Now that we have the dominant eigenvalue when $\sigma = 0$, we wish to approximate the dominant eigenvalue when σ is assumed to be small. Let us denote the characteristic equation of the matrix J_A by $f(\lambda) = 0$. Where λ is the dominant eigenvalue of the characteristic equation. We begin by assuming that we can write the eigenvalue in powers of σ,

$$\lambda = \lambda_0 + \lambda_1\sigma + \lambda_2\sigma^2 + \lambda_3\sigma^3... \tag{3.21}$$

We then substitute in our equation for λ into the characteristic equation to obtain

$$f\left(\lambda_0 + \lambda_1\sigma + \lambda_2\sigma^2 + \lambda_3\sigma^3\ ..\right) = 0.$$

We then Taylor expand our characteristic equation in powers of σ, about the point $\sigma = 0$ to obtain

$$f\left(\lambda_0 + \lambda_1\sigma + \lambda_2\sigma^2 + \lambda_3\sigma^3\ ..\right) = f|_{\sigma=0} + \frac{df}{d\sigma}|_{\sigma=0}\sigma + \frac{1}{2}\frac{d^2f}{d\sigma^2}|_{\sigma=0}\sigma^2... = 0.$$

Notice that if λ is exact then each term in our taylor expansion should equal zero; therefore we can use these equations to solve for the constants $\lambda_0, \lambda_1..$ and obtain an approximation for λ in powers of σ.

Since we are interested in the behaviour when sigma is small, we will only expand to order 1: $\lambda = \lambda_0 + \lambda_1\sigma$, we will call this new quantity $\hat{r}_C$. $\hat{r}_C$ is an approximation of the eigenvalue when coinfection is permitted; i.e., r_C for small σ.

$$\hat{r}_c = r_S + \lambda_1\sigma \tag{3.22}$$

We note that as long as σ is sufficiently small enough we have that

$$\hat{r}_C(\sigma) > r_S \Rightarrow r_C(\sigma) > r_S. \tag{3.23}$$

Therefore we can use $\hat{r}_C$ to determine the effect of coinfection, for σ, relative to r_S. Preceding in the manner described above, for each set of parameter assumptions in Table 3.1, we obtain the following approximations for the dominant eigenvalue of the system of equations 2.4 when σ is assumed to be sufficiently small.

Table 3.4: $\hat{r}_C$ for the cost of resistance cases.

	$\hat{r}_C$
NC	$\nu + -\frac{\nu(5\nu+3\mu_B)(-\Theta\beta_B+\mu(\nu+\mu_B))}{2(\nu+\mu_B)(2\nu+\mu_B)^2}(\sigma)$
RT	$r = \frac{\nu\beta_A+\beta_A\mu_B-\beta_B\mu_B}{\beta_B} - \frac{\beta_A(-\Theta\beta_B+\mu(\nu+\mu_B))\left(2\nu^2\beta_B^2+\beta_A^2(\nu+\mu_B)^2+\beta_A\beta_B\left(2\nu^2+\nu\mu_B-\mu_B^2\right)\right)}{2\beta_B(\nu+\mu_B)(\nu\beta_B+\beta_A(\nu+\mu_B))^2}(\sigma)$
RG	$r = \frac{\nu\beta_A-\beta_B\mu_A+\beta_A\mu_B}{\beta_B} + -\frac{\beta_A(-\Theta\beta_B+\mu(\nu+\mu_B))\left(\beta_A(\nu+\mu_B)(\nu\phi+(-1+\phi)\mu_B)+\beta_B\left(\nu^2(1+2\phi)+\nu(-1+3\phi)\mu_B+(-1+\phi)\mu_B^2+\mu_A(\nu+\mu_B)\right)\right)}{(\nu+\mu_B)(\nu\beta_B+\beta_A(\nu+\mu_B))(\beta_A(\nu+\mu_B)+\beta_B(\nu-\mu_A+\mu_B))}(\sigma)$
PC	$r = \nu - \frac{\left(\nu^2(1+3\phi)+\nu(-1+5\phi)\mu_B+(-1+2\phi)\mu_B^2\right)(-\Theta\beta_B+\mu(\nu+\mu_B))}{(\nu+\mu_B)(2\nu+\mu_B)^2}(\sigma)$
IM	$r = \nu - \mu_A + \mu_B + -\frac{(-\Theta\beta_A+\mu(\nu+\mu_B))\left(5\nu^2+2\nu\mu_B-\mu_B^2+\mu_A(\nu+\mu_B)\right)}{(4\nu-\mu_A+3\mu_B)\left(2\nu^2+3\nu\mu_B+\mu_B^2\right)}(\sigma)$

Refering to table 3.4 for the no cost of resistance case and using the fact that

$$\hat{h}_B = \Theta\left(\frac{\nu\beta_{\mathrm{TB}}}{(\nu+\mu_B)(\mu_{\mathrm{TB}})} + \frac{\beta_B}{(\nu+\mu_B)}\right) - \mu = \Theta\frac{\beta_B}{(\nu+\mu_B)} - \mu > 0$$

it is trivial to show that λ_1, the constant multiplying σ, is always positive. Therefore we have that, for σ sufficiently small, coinfection will increase the intrinsic rate of growth of the resistant strain. For the reduced transmission case, we again can show that $\lambda_1 > 0$ since $\hat{h}_B > 0$. So again, for the reduced transmission case we have that $\hat{r}_c > r_S$. For the reduced growth case we have that $-\Theta\beta_B + \mu(\nu+\mu_B) > 0$ since $\hat{h}_B > 0$ however the term

$$\begin{aligned}&\beta_A(\nu+\mu_B)(\nu\phi+(-1+\phi)\mu_B) + \\ &\beta_B\left(\nu^2(1+2\phi)+\nu(-1+3\phi)\mu_B+(-1+\phi)\mu_B^2+\mu_A(\nu+\mu_B)\right)\end{aligned}$$

can be less than or greater than 0 depending on the parameter values. Therefore we cannot determine the magnitude of r_S relative to r_C. For the poor competitor case, again we have instances were $r_S < \hat{r}_c$ and $\hat{r}_c > r_S$ therefore λ_1 can be greater than or equal to zero. Therefore for σ sufficiently small coinfection can increase or decrease the intrinsic rate of growth. For the increased mortality case we have that since $\hat{h}_B > 0$, $-\Theta\beta_A + \mu(\nu+\mu_B) < 0$. Also, $\frac{\left(5\nu^2+2\nu\mu_B-\mu_B^2+\mu_A(\nu+\mu_B)\right)}{(4\nu-\mu_A+3\mu_B)} > 0$ since $\mu_A > \mu_B$. Therefore for the increased mortality case we have that $\hat{r}_c > r_S$. We summarize these results in table 4.2

Notice that we get similar relative behaviour between r_C and r_S versus R_C and R_S, refer to figure 3.5. As a result we present the following conjecture:

Conjecture III.1. *If strain A and strain B differ in only one parameter then for* $\sigma > 0$ $R_C > R_S \Rightarrow r_C > r_S$

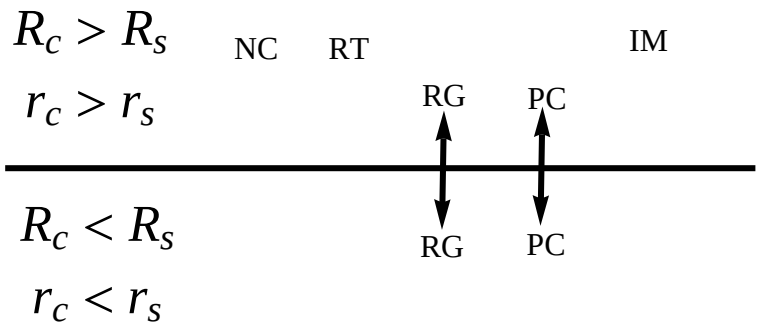

Figure 3.5: Behaviour of R_0 compared to the intrinsic growth rate for the coinfection and single infection case. We obtain similar relative behaviour between r_C and r_S versus R_C and R_S. Where NC is the no cost of resistance case, RG is the reduced growth case, RT is the reduced transmission case, PC is the poor competitor case and IM is the increased mortality case.

Table 3.5: r_C versus r_S for various costs of resistance.

	Sign of λ_1	Effect of Coinfection for small σ
No Cost (NC)	> 0 since $\hat{h}_B > 0$	$r_C > r_S$
Reduced Transmission (RT)	> 0 since $\hat{h}_B > 0$	$r_C > r_S$
Reduced Growth(RG)	> 0 or < 0 depending on parameter values	$r_C > r_S$ or $r_S > r_C$
Poor Competitor (PC)	> 0 or < 0 depending on parameter values	$r_C > r_S$ or $r_S > r_C$
Increased Mortality (IM)	> 0 since $\mu_A > \mu_B$ and $\hat{h}_B > 0$	$r_C > r_S$

Since r_C is the rate of growth of A propagules, when we are near the endemic B equilibrium, we can approximate the percentage of resistant propagules when σ is small, (PRC), as a function of time with the following equation:

$$PRC = \frac{h_A[0] \exp \hat{r}_C t}{h_A[0] \exp \hat{r}_C t + \hat{h}_B} * 100, \tag{3.24}$$

where $h_A[0]$ is the force of infection of the A strain when $t = 0$; the initial number of A propagules introduced into the population at time $t = 0$. When single infections only are permitted $\sigma = 0$ and the percentage of resistance as a function of time, (PRS) can be approximated with the following equation:

$$PRS = \frac{h_A[0] \exp r_S t}{h_A[0] \exp r_S t + \hat{h}_B} * 100 \tag{3.25}$$

Since we are only interested in the regime near the endemic equilibrium we assume that $h_B \approx \hat{h}_B$. We plot the percent resistance, in figure 3.6 and 3.7 versus time for the various cost of resistance cases given in Table 3.1 for a particular set of parameters.

In this section we have shown a method of estimating the intrinsic rate of growth when σ, the coinfection efficiency is small. For the increased mortality, reduced transmission and no cost of resistance cases, coinfection increases the intrinsic rate

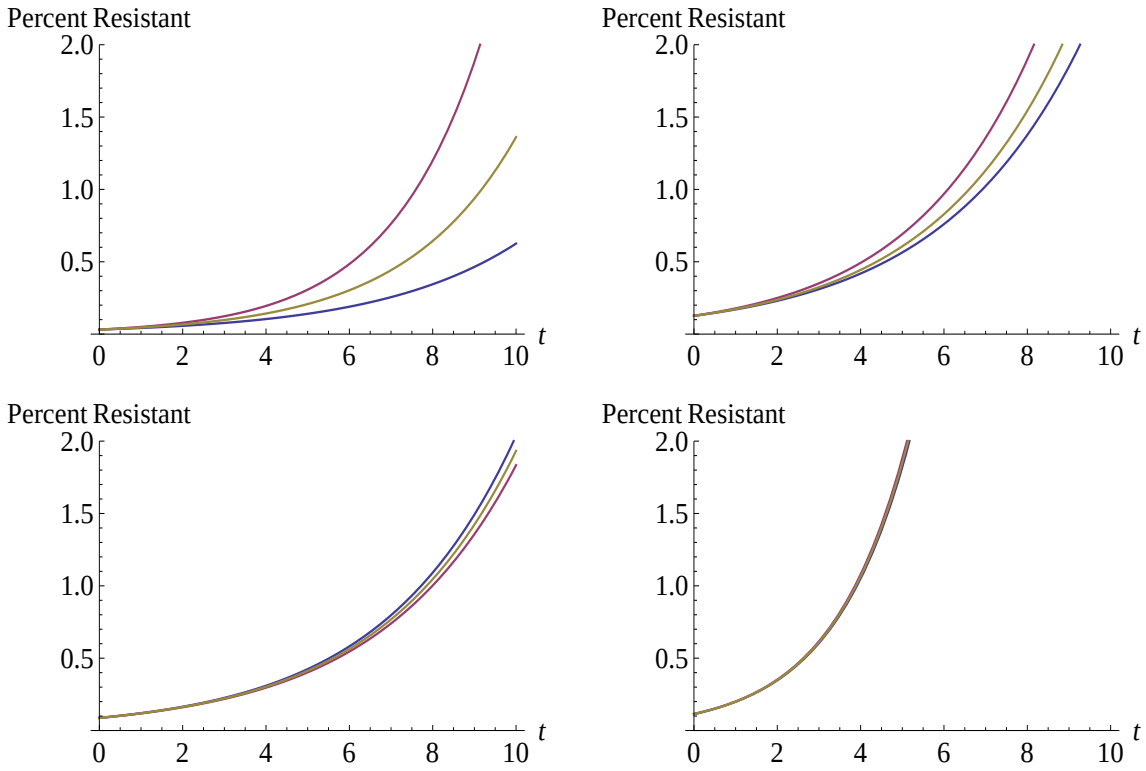

Figure 3.6: Percent resistance as a function of time for no cost of resistance, and reduced transmission and reduced growth cost of resistance. $\frac{h_A[0]\exp rt}{h_A[0]\exp r_{ct}+\hat{h}_B}100$ *vs.* t, red line estimate of percent resistance using $r = \hat{r}_C$ for $\sigma = 0.01$. Yellow line estimate of percent resistance using $r = \hat{r}_C$, $\sigma = 0.005$. Blue line estimate of percent resistance for single infections $r = r_S$. Top left: No Cost of Resistance $\Theta = 20$, $\mu = 0.1$, $\beta_B = 0.8$, $\beta_A = 0.8$, $\mu_B = 0.2$, $\mu_A = 0.2$, $\nu = 0.3$, $h_A[0] = 0.01$. Top Right: Cost of Resistance Reduced Transmission $\Theta = 10$, $\mu_0.1$, $\beta_B = 0.4$, $\beta_A = 0.3$, $\mu_B = 0.2$, $\mu_A = 0.2$, $\nu = 0.3$, $h_A[0] = 0.01$. Bottom Left: Cost of Resistance Reduced Growth $\hat{r}_C > r_S$ $\Theta = 20$, $\mu_0.4$, $\beta_B = \frac{129}{256}$, $\beta_A = \frac{31}{64}$, $\mu_B = 0.6$, $\mu_A = 0.5$, $\nu = 0.25$, $\phi = 1/4$, $h_A[0] = 0.01$. Bottom Right: Cost of Resistance Reduced Growth $r_S > r_C$ $\Theta = 20$,$\mu = 0.4$, $\beta_B = \frac{129}{256}$, $\beta_A = \frac{31}{64}$, $\mu_B = 0.6$, $\mu_A = 0.5$, $\nu = 0.4$, $\phi = 1/4$,$\nu = \frac{1}{2}$,$h_A[0] = 0.01$

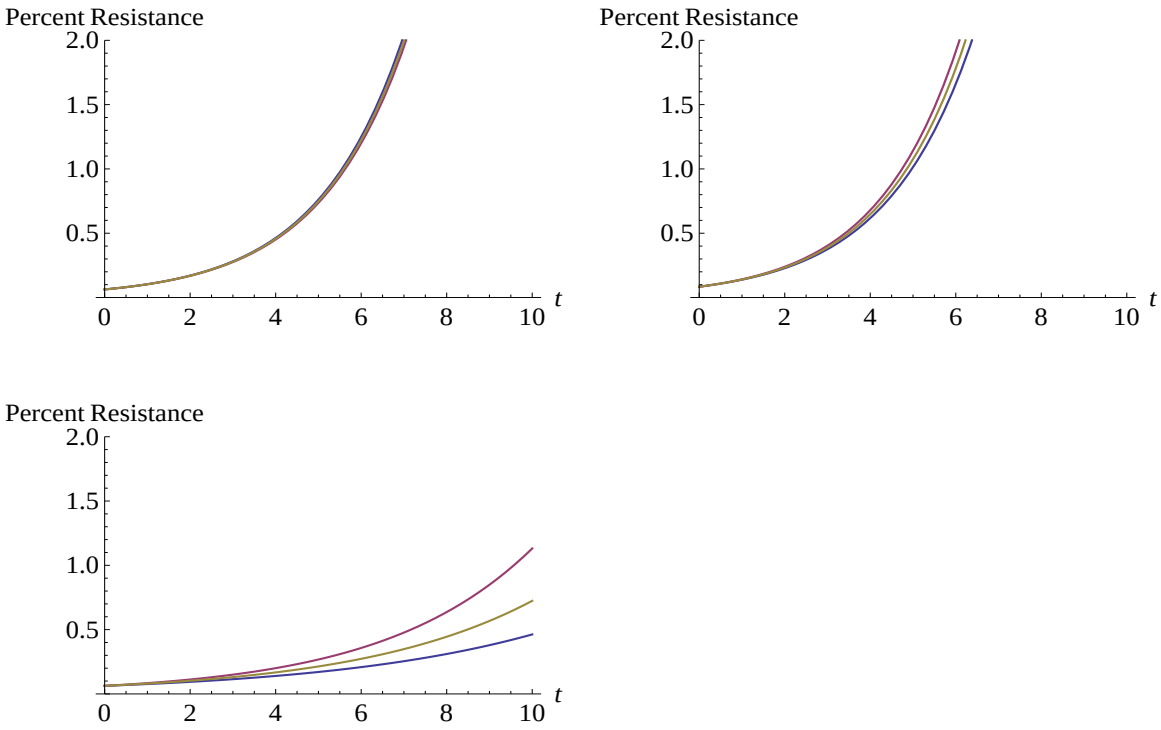

Figure 3.7: Percent Resistance versus time for poor competitor and increased mortality cost of resistance. $\frac{h_A[0]\exp rt}{h_A[0]\exp r_{ct}+\hat{h}_B}100$ *vs.* t, red Line estimate of percent resistance using $r = r_C$ for $\sigma = 0.01$. Yellow line estimate of percent resistance using $r = r_C$, $\sigma = 0.005$. Blue line estimate of percent resistance for single infections $r = r_S$. Top left: Cost of Resistance Poor Competitor,$r_C > r_S$, $\Theta = 40$, $\mu = 0.1$, $\beta_B = 0.4$, $\beta_A = 0.4$, $\mu_B = 0.5$, $\mu_A = 0.5$, $\nu = 0.5$, $\psi = \frac{1}{16}$, $h_A[0] = 0.01$. Top Right: Cost of Resistance Poor Competitor $r_S > r_C$ $\Theta = 30$, $\mu = 0.1$, $\beta_B = 0.4$, $\beta_A = 0.4$, $\mu_B = 0.5$, $\mu_A = 0.5$, $\nu = 0.5$, $\phi = \frac{9}{32}$, $h_A[0] = 0.01$. Bottom Left: Cost of Resistance Increased Mortality $\Theta = 20$, $\mu = 0.1$, $\beta_B = 0.4$, $\beta_A = 0.4$, $\mu_B = 0.2$, $\mu_A = 0.3$, $\nu = 0.3$

of growth, near the endemic equilibrium, when the coinfection efficiency is sufficiently small and can either increase or decrease intrinsic rate of growth for the poor competitor and reduced growth cases. Recall, that this is the same result obtained for r_C vs. r_S. It follows then that if the coinfection efficiency is sufficiently small and if the cost of resistance is no cost, reduced transmission or increased mortality then the presence of coinfection will cause the resistant strain to reach higher levels of resistance faster than if there was only single infection. Intervention strategies that reduce the amount of coinfection could then potentially reduce the speed at which resistant strains grow, and therefore lengthen the practical lifetime of a drug.

CHAPTER IV

The Effect of Changing Treatment Rate

Now that we know how coinfection effects the R_0 values and the intrinsic growth rate, we are interested in determining how changing the treatment rate, ν, will change R_0 and the intrinsic growth rate, r, in the coinfection case relative to the single infection case. In other words, will increasing the treatment rate increase R_C more or less than R_S? Likewise, will increasing treatment rate, ν, increase r_c more or less than r_s? This is a conspicious question for public health planners, as intervention strategies such as increasing the rate of treatment could, potentially, have a greater effect on the increase of drug resistance depending on the amount of coinfection present. Alternatively, depending on the level of coinfection, it is possible that a population will be more robust, (the increase in resistance is less than it would be if there were single infections only), to increases in the treatment rate.

4.1 Effect of Change in Coverage Rate on R_0

We will begin by examining the effect of a change in coverage rate on R_C relative to R_S. Recall from section 1.3, that we have previously defined the quantities w, and g such that we can express the R_C value for an invading resistant mutant in the following form:

$$R_C[\nu] = R_S[\nu]\left(w[\nu] + (1 - w[\nu])g[\nu]\right), \tag{4.1}$$

where we have now explicitly indicated the dependence on ν. Now let us define a new quantity $M[\nu]$ as:

$$M[\nu] = (w[\nu] + (1 - w[\nu])g[\nu])$$

and rewrite our expression R_C as:

$$R_C[\nu] = R_S[\nu]M[\nu].$$

We note that $M[\nu]$ is the factor by which R_C differs from R_S.

Differentiating R_C with respect to ν we obtain:

$$\frac{\partial R_C}{\partial \nu} = \frac{\partial R_s}{\partial \nu}M[\nu] + \frac{\partial w}{\partial \nu}\left(1 - g[\nu]\right)R_S[\nu] + \frac{\partial g}{\partial \nu}\left(1 - w[\nu]\right)R_S[\nu] \tag{4.2}$$

We notice that since we can view R_C as a function of w, R_S and g, and since w, R_S and g are in turn functions of ν, we can apply the chain rule to obtain the following alternative expressions for $\frac{\partial R_C}{\partial \nu}$:

$$\frac{\partial R_C}{\partial \nu} = \frac{\partial R_S}{\partial \nu}\frac{\partial R_C}{\partial R_S} + \frac{\partial g}{\partial \nu}\frac{\partial R_C}{\partial g} + \frac{\partial w}{\partial \nu}\frac{\partial R_C}{\partial w}, \tag{4.3}$$

where:

$$\frac{\partial R_C}{\partial R_S} = M[\nu] \tag{4.4}$$

$$\frac{\partial R_C}{\partial g} = \left(1 - g[\nu]\right)R_S[\nu] \tag{4.5}$$

$$\frac{\partial R_C}{\partial g} = \left(1 - w[\nu]\right)R_S[\nu] \tag{4.6}$$

.

Examining, expression 4.3 we see that we can view the change in R_C with respect to ν as a combination of how a change in R_S with respect to ν contributes to a change in R_C, how a change in g with respect to ν contributes to a change in R_C and how a change in w with respect to ν contributes to a change in R_C.

Since we are interested in how the R_0 value in a coinfection case changes compared to the R_0 value in a single infection case, we are in fact interested in the difference of the derivatives, $\frac{\partial R_C}{\partial \nu}$ and $\frac{\partial R_S}{\partial \nu}$.

$$\begin{aligned} \frac{\partial R_C}{\partial \nu} - \frac{\partial R_S}{\partial \nu} &= \frac{\partial R_S}{\partial \nu}\frac{\partial R_C}{\partial R_S} + \frac{\partial g}{\partial \nu}\frac{\partial R_C}{\partial g} + \frac{\partial w}{\partial \nu}\frac{\partial R_C}{\partial w} - \frac{\partial R_S}{\partial \nu} \\ &= \frac{\partial R_S}{\partial \nu}\left(\frac{\partial R_C}{\partial R_S} - 1\right) + \frac{\partial g}{\partial \nu}\frac{\partial R_C}{\partial g} + \frac{\partial w}{\partial \nu}\frac{\partial R_C}{\partial w} \end{aligned} \tag{4.7}$$

Let us label the terms of 4.8 $T1$, $T2$ and $T3$ respectively; i.e.,

$$\begin{aligned} T1 &= \frac{\partial R_S}{\partial \nu}\left(\frac{\partial R_C}{\partial R_S} - 1\right) = \frac{\partial R_s}{\partial \nu}\left(M[\nu] - 1\right) \\ T2 &= \frac{\partial g}{\partial \nu}\frac{\partial R_C}{\partial g} = \frac{\partial g}{\partial \nu}\left(1 - w[\nu]\right) R_S[\nu] \\ T3 &= \frac{\partial w}{\partial \nu}\frac{\partial R_C}{\partial w} = \frac{\partial w}{\partial \nu}\left(1 - g[\nu]\right) R_S[\nu] \end{aligned}$$

Examining expression 4.8 term by term we can gain a better understanding of how R_C changes with ν compared to how R_S changes with ν.

Let us begin by examining T1. First we note that $\frac{\partial R_S}{\partial \nu}$ is given by the following expression:

$$\frac{\partial R_S}{\partial \nu} = \frac{\beta_A}{\beta_B \mu_A}. \tag{4.8}$$

This quantity will always be positive. This is what we would expect, since in the single infection case increasing treatment will increase the advantage of the A strain, (less competition from the B strain), thus increasing its R_0 value. Therefore, the sign of T1 will be determined by $M-1$. Recall that M gives how R_C changes with respect to a change in R_S (from 4.4). If coinfection increases R_C then g will be greater than one. Now since $g>1 \leftrightarrow M>1$, $T1$ will be positive. Alternatively if coinfection decreases R_0 then $M>1$ and therefore $T1<1$.

T2 gives how a change in g with respect ν, will contribute to $\frac{\partial R_C}{\partial \nu}$. Recall, from 3.10, that

$$g = fk.$$

Differentiating g with respect to ν we therefore have that:

$$\frac{\partial g}{\partial \nu} = \frac{\beta_A\mu_{\mathrm{AB}}-\mu_A\beta_{\mathrm{AB},A}}{\beta_A(\nu+\mu_{\mathrm{AB}})^2}\left(1+\frac{\nu+\sigma h_B[\nu]+\mu_A}{\nu+\sigma h_B[\nu]+\mu_B}\right) + -\frac{(\mu_A-\mu_B)\left(-\Theta\sigma\beta_B+(\nu+\mu_B)^2\right)}{(\Theta\sigma\beta_B+(\nu+\mu_B)(\nu-\mu\sigma+\mu_B))^2}\frac{\left(\beta_{\mathrm{AB},A}\mu_A+\nu\beta_A\right)(\nu+\mu_A)(\mu_A)}{(\nu+\mu_{\mathrm{AB}})(\mu_A)(\beta_A\mu_A+\nu\beta_A)}$$

We note that the magnitude of g depends on the sign of $\frac{\partial f}{\partial \nu}$ and $\frac{\partial k}{\partial \nu}$. We have that $\frac{\partial f}{\partial \nu}$ will can be positive or negative depending on the particular parameter relationships. Likewise $\frac{\partial k}{\partial \nu}$ can be negative, positive or zero depending on the particular parameter choices. If $\mu_A=\mu_B$ the fraction of I_{AB} infections versus I_{BA} infections will remain constant and $\frac{\partial k}{\partial \nu}=0$. Otherwise the sign of $\frac{\partial k}{\partial \nu}$ will depend on the sign of $\mu_A-\mu_B$ as well as the sign of $(-\Theta\sigma\beta_B+(\nu+\mu_B)^2)$. In general we have:

$$\frac{\partial k}{\partial \nu} = -\frac{(\mu_A-\mu_B)\left(-\Theta\sigma\beta_B+(\nu+\mu_B)^2\right)}{(\Theta\sigma\beta_B+(\nu+\mu_B)(\nu-\mu\sigma+\mu_B))^2}.$$

Table 4.1 gives the expressions for $\frac{\partial k}{\partial \nu}$ and $\frac{\partial f}{\partial \nu}$, and the sign of $\frac{\partial g}{\partial \nu}$ for the various cost of resistance cases.

Now $\frac{\partial R_C}{\partial g}>0$ will always be greater than zero, therefore if $\frac{\partial g}{\partial \nu}>0$ then $T2>0$. This

Table 4.1: Change in k, f and g with respect to ν for the various cost of resistance cases.

	$\frac{\partial k}{\partial \nu}$	$\frac{\partial f}{\partial \nu}$	$\frac{\partial g}{\partial \nu}$
NC	0	$\frac{\frac{1}{2}\mu_B}{(\nu+\mu_B)^2} > 0$	> 0
RT	0	$\frac{\frac{1}{2}\mu_B}{(\nu+\mu_B)^2} > 0$	> 0
RG	$-\frac{(\mu_A-\mu_B)\left(-\Theta\sigma\beta_B+(\nu+\mu_B)^2\right)}{(\Theta\sigma\beta_B+(\nu+\mu_B)(\nu-\mu\sigma+\mu_B))^2}$	$\frac{\beta_A\mu_B-\mu_A\phi\beta_B}{\beta_A(\nu+\mu_B)^2}$	Indeterminate
PC	0	$-\frac{(-1+\phi)\mu_A}{(\nu+\mu_A)^2} > 0$	> 0
IM	$-\frac{(\mu_A-\mu_B)\left(-\Theta\sigma\beta_B+(\nu+\mu_B)^2\right)}{(\Theta\sigma\beta_B+(\nu+\mu_B)(\nu-\mu\sigma+\mu_B))^2}$	$\frac{2\mu_B}{(2\nu+\mu_A+\mu_B)^2} > 0$	Indeterminate

makes sense, as we would expect that if the advantage of coinfection increases with treatment $\frac{\partial g}{\nu} > 0$ then this will contribute to an increase in R_C.

T3 gives how changing w with respect to ν effects $\frac{\partial R_C}{\partial \nu}$. Recall, from (3.9), that

$$w = \frac{\nu + \mu_A}{\nu + \mu_A + \hat{h}_B[\nu]}$$

which is the fraction of single A infections, that do not become coinfected. Differentiating w, with respect to ν we obtain,

$$\frac{\partial w}{\partial \nu} = \frac{\sigma\left(-\mu\left(\nu+\mu_B\right)^2 + \Theta\beta_B\left(2\nu+\mu_A+\mu_B\right)\right)}{\left(\Theta\sigma\beta_B + \left(\nu-\mu\sigma+\mu_A\right)\left(\nu+\mu_B\right)\right)^2}. \tag{4.9}$$

We notice that the denominator of 4.9 will always be positive and that the numerator of 4.9 will be positive if the following inequality holds,

$$\frac{\theta\beta_B}{\nu+\mu_B} > \mu\frac{\nu+\mu_B}{2\nu+\mu_A+\mu_B}. \tag{4.10}$$

Since $\hat{h}_B > 0$ and $\frac{\nu+\mu_B}{2\nu+\mu_A+\mu_B} < 1$, 4.10 will always hold and therefore $\frac{\partial w}{\partial \nu} > 0$. This is what we would expect, since as we increase the treatment rate, I_A infections will be

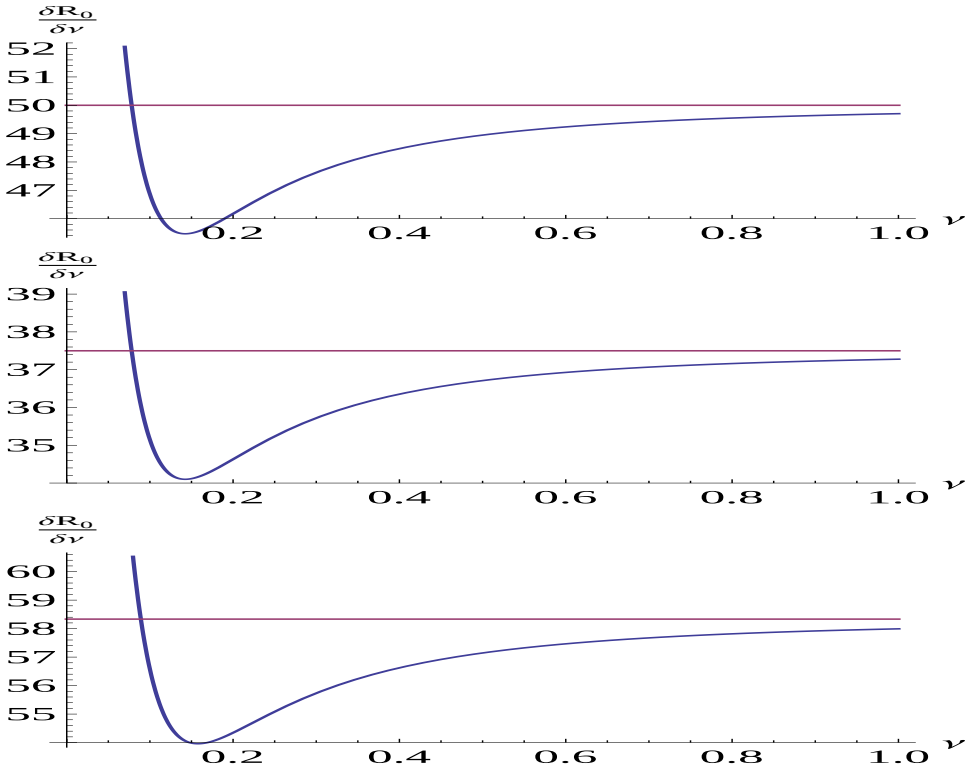

Figure 4.1: Change in R_0 vs. treatment rate as a function of treatment rate for the no cost of resistance case, and reduced transmission and reduced growth cost of resistance. Single infection case (red line) and coinfection case (blue line). $\frac{\partial R_s}{\partial \nu}$ is constant with ν, whereas $\dot{R}_c$ varies with ν. Top: No Cost of Resistance Case $\Theta = 1$, $\beta_B = \frac{1}{2}$, $\mu = \frac{1}{16}$,$\mu_B = \frac{3}{16}$,$\sigma = \frac{9}{16}$. Center: Reduced Transmission Cost of Resistance $\Theta = 3$, $\beta_B = \frac{1}{2}$, $\beta_A = \frac{1}{3}$, $\mu = \frac{1}{8}$, $\mu_B = \frac{1}{4}$, $\sigma = \frac{1}{1}$. Bottom: Reduced Growth Cost of Resistance $\Theta = 2$, $\beta_B = 0.8$, $\beta_A = 0.7$, $\mu = \frac{1}{8}$, $\mu_B = \frac{1}{4}$, $\mu_A = \frac{1}{5}$, $\phi = \frac{1}{3}$, $\sigma = 0.1$.

more likely to become treated before they have the opportunity to become coinfected. The sign of $T2$ will therefore be determined by the sign of $\frac{\partial R_C}{\partial w} = (1 - g[\nu])\, R_S[\nu]$. If coinfection increases R_C, $(g > 1)$, $T2$ will be < 0, since an increase in the fraction of single infections, (w) will result in a reduction of the advantageous coinfection, therefore reducing R_C. If coinfection decreases the R_C value, $(g < 1)$, $T2$ will be > 0 since an increase in the fraction of single infections will result in a reduction of the disadvantageous coinfection therefore increasing R_C. We plot parameter instances of these cases in figure 4.1 and figure 4.2.

From figure 4.1 top left we see that for $\nu = 0$, $\frac{\partial R_0}{\partial \nu} > \frac{\partial R_S}{\partial \nu}$ but as ν increases

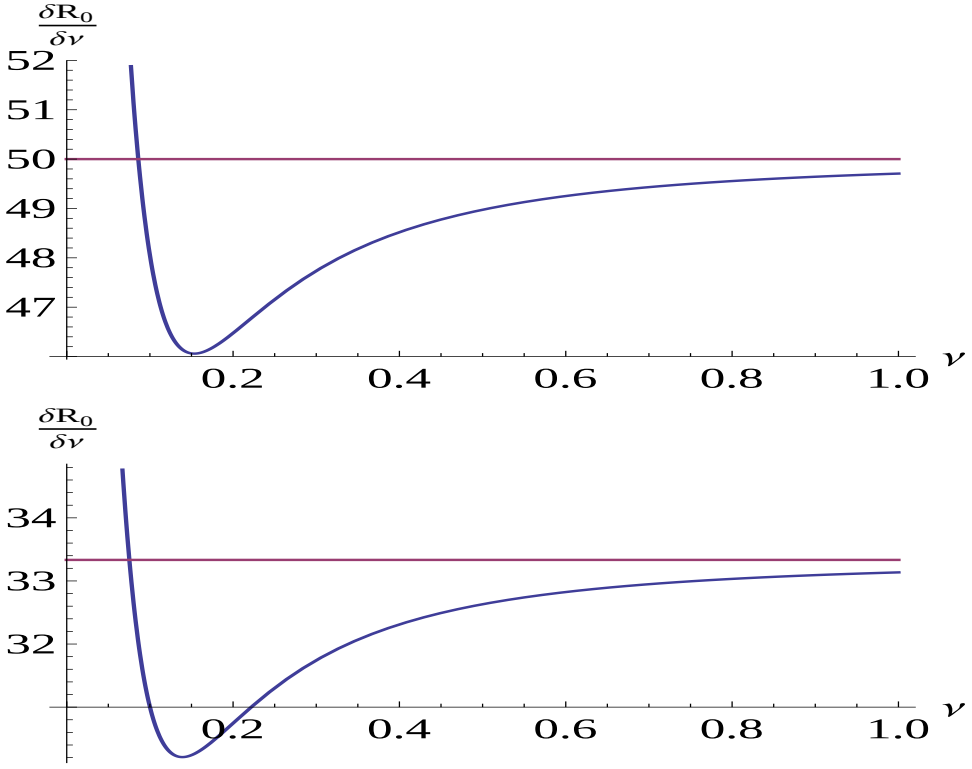

Figure 4.2: Change in R_0 vs. treatment rate as a function of treatment rate for the poor competitor and increased mortality cost of resistance. $\frac{\partial R_0}{\partial \nu}$ vs. ν for single infection case (red line) and coinfection case (blue line), $\frac{\partial R_s}{\partial \nu}$ is constant with ν, whereas $\dot{R}_c$ varies with ν. Top: Poor Competitor Cost of Resistance Case $\Theta = 2$, $\beta_B = 0.8$, $\mu = \frac{1}{8}$, $\mu_B = \frac{1}{4}$, $\phi = \frac{1}{3}$, $\sigma = 0.1$. Bottom: Increased Mortality Cost of Resistance $\Theta = 2$, $\beta_B = 0.8$, $\mu = 0.2$, $\mu_B = 0.3$, $\mu_A = 0.4$, $\sigma = 0.1$.

there is a point of intersection, $\nu*$ where $\frac{\partial R_0}{\partial \nu} = \frac{\partial R_S}{\partial \nu}$ and then $\frac{\partial R_0}{\partial \nu} < \frac{\partial R_S}{\partial \nu}$. Therefore depending on the parameter choices and the treatment rate, R_0 in the coinfection case can either increase more quickly or less quickly than in the single infection case. In other words, coinfection can either diminish or enhance the effect of increasing the treatment rate. We get prescisely the same result for the reduced transmission, reduced growth, poor competitor case and increased mortality cases as well.

We also note that if we take the limit of R_C as ν becomes large we get

$$\lim_{\nu \to +\infty} \frac{\partial R_C}{\partial \nu} = \frac{\beta_A}{\beta_B \mu_A}. \tag{4.11}$$

$$\lim_{\nu \to +\infty} \frac{\partial R_S}{\partial \nu} = \frac{\beta_A}{\beta_B \mu_A}. \tag{4.12}$$

Comparing 4.11 to the limit of $\frac{\partial R_S}{\partial \nu}$ as the treatment rate, ν, becomes large, equation 4.12, we see that both have the same limiting behaviour. This is what we would expect since as we increase treatment, the fraction of those single infections, I_A, that do not become infected approaches 1, and the derivative $\frac{\partial w}{\partial \nu}$ approaches zero. In addition the parameter who's value compared to 1 determines the effect of coinfection, g, approaches 2 and it's derivative approaches zero.

Therefore we can conclude that depending on the particular choice of parameters coinfection could, potentially make the emergence of resistance more robust to increases in treatment, i.e. R_C will increase slower than R_S. Conversely coinfection could result in the emergence of resistance being more sensitive to increases in treatment, meaning that R_C will change more than R_S. We note that when treatment becomes sufficiently large $\frac{\partial R_S}{\partial \nu} \approx \frac{\partial R_C}{\partial \nu}$, and R_C and R_S will change, with respect to increasing treatment, at a similar rate.

4.2 Effect of Change in Coverage Rate on the intrinsic growth rate (r)

Recall that we can expand the growth rate in powers of σ and therefore the intrinsic growth rate can be written as,

$$r = m(\nu) + n(\nu) * \sigma + O \tag{4.13}$$

where "O" represents the higher order terms. For cases where σ is sufficiently small then whether the intrinsic growth rate increases or decreases with a change in ν can simply be determined by looking at the derivative of the first term of r, $\frac{\partial m}{\partial \nu}$. For σ small enough this should be sufficient to determine the sign of $\frac{\partial r}{\partial \nu}$ assumming that each consecutive term in the power series is bounded with respect to differentiation in ν. Table 4.2 gives derivatives of r_S with respect to ν for the various costs of resistance. As long as we choose σ sufficiently small enough we see that $\frac{\partial r}{\partial \nu}$ will always be positive.

Table 4.2: $\frac{\partial r_S}{\partial \nu}$ for different cost of resistance cases.

	$\frac{\partial r_S}{\partial \nu}$
No Cost (NC)	1
Reduced Transmission (RT)	$\frac{\beta_A}{\beta_B}$
Reduced Growth(RG)	$\frac{\beta_A}{\beta_B}$
Poor Competitor (PC)	1
Increased Mortality (IM)	1

The derivative of $\frac{\partial n}{\partial \nu}$ with respect to ν for the various costs of resistance is very long and not very elucidating, we therefore omit it here. However, figure 4.3 and figure 4.4 plot parameter instances for $\frac{\partial \hat{r}_C}{\partial \nu}$ versus ν, as well as $\frac{\partial r_S}{\partial \nu}$ for particular parameter instances. From figure 4.3 and figure 4.4, we see that similarily to the

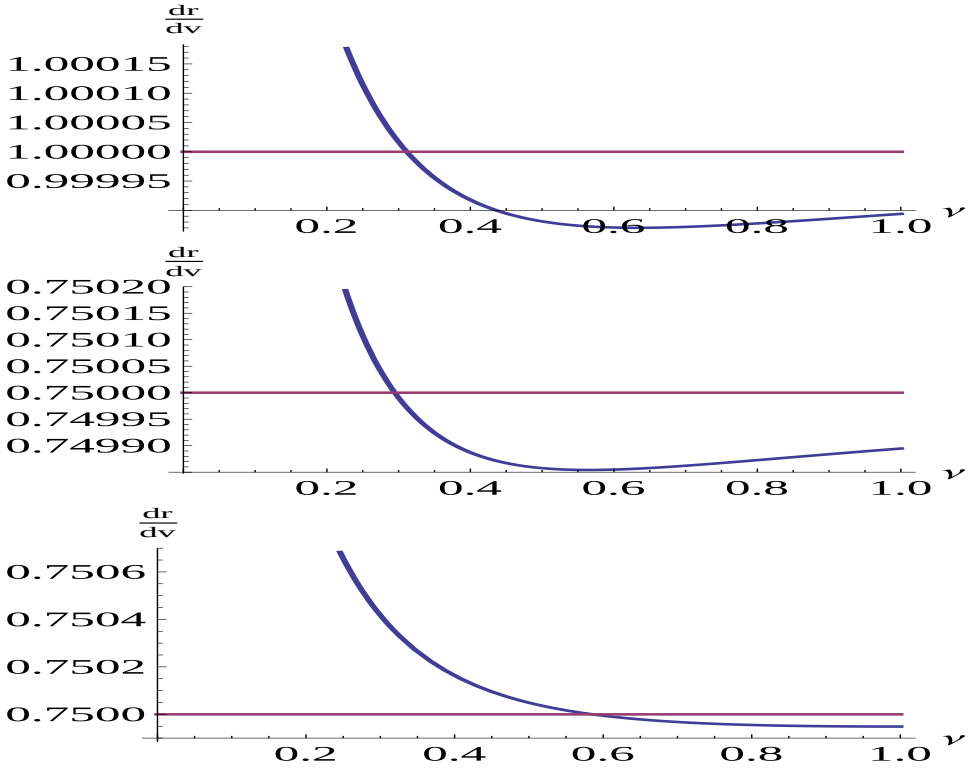

Figure 4.3: The change in the intrinsic rate of growth versus treatment rate as a function of treatment rate for the no cost of resistance case and reduced transmission and reduced growth cost of resistance cases. Single infection case (red line) and coinfection case (blue line), $\frac{\partial r_S}{\partial \nu}$ is constant with ν, whereas $\frac{\partial \hat{r}_c}{\partial \nu}$ varies with ν. Top: No Cost of Resistance Case $\Theta = 3$, $\beta_B = 2$, $\mu = 0.3$, $\mu_B = 0.5$, $\sigma = 0.01$. Center: Reduced Transmission Cost of Resistance $\Theta = 3$, $\beta_B = 2$, $\beta_A = 1.5$, $\mu = 0.3$, $\mu_B = 0.4$, $\sigma = 0.01$. Bottom: Reduced Growth Cost of Resistance $\Theta = 3$, $\beta_B = 2$, $\beta_A = 1.5$, $\mu = 0.3$, $\mu_B = 0.4$, $\mu_A = 0.35$, $\phi = \frac{1}{3}$, $\sigma = 0.01$.

derivative of R_C and R_S, $\frac{\partial \hat{r}_c}{\partial \nu}$ can be greater than or equal to $\frac{\partial r_S}{\partial \nu}$ depending on the particular choice of parameters.

Therefore, similar to the $\frac{\partial R_C}{\partial \nu}$ analysis we can conclude that depending on the particular choice of parameters coinfection could, potentially make the growth of resistance more robust to increases in treatment, i.e. r_c will increase slower than r_S. Or coinfection could result in the growth of resistance being more sensitive to increases in treatment, meaning that r_C will change more than r_S.

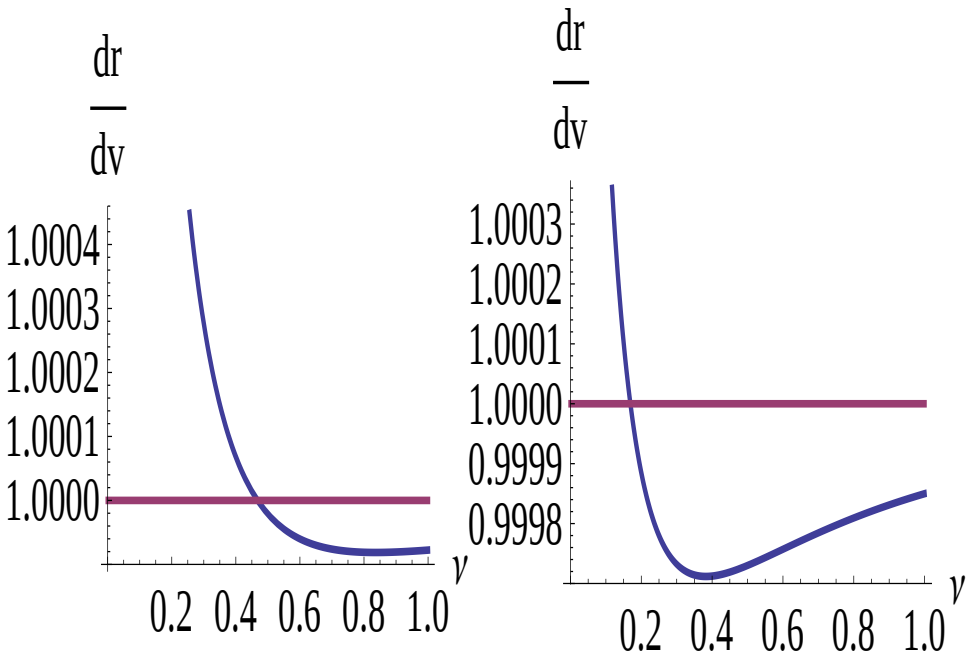

Figure 4.4: The change in the intrinsic rate of growth versus treatment rate as a function of treatment rate for the poor competitor and increased mortality cost of resistance cases. $\frac{\partial r}{\partial \nu}$ versus ν for single infection case (red line) and coinfection case (blue line), $\frac{\partial r_S}{\partial \nu}$ is constant with ν, whereas $\frac{\partial \hat{r}_c}{\partial \nu}$ varies with ν. Left: Poor Competitor Cost of Resistance Case $\Theta = 3$, $\beta_B = 2$, $\mu = 0.3$, $\mu_B = 0.4$, $\phi = \frac{1}{3}$, $\sigma = 0.01$. Right: Increased Mortality Cost of Resistance $\Theta = 3$, $\beta_B = 2$, $\mu = 0.3$, $\mu_B = 0.4$, $\mu_A = 0.5$, $\sigma = 0.01$.

CHAPTER V

Conclusion

In this thesis we have formulated a multiple infection model with treatment and derived the conditions for invasion. We have shown that the invasion condition is equivalent to an often easier to obtain condition, R_0 by applying the Next-Generation Theorem. Then assuming that resistance comes at a cost to the pathogen and using a very simple within-host model we established under which specific set of biological assumptions we should expect coinfection to increase or decrease R_0. Specifically, we obtained that in the no cost of resistance case, reduced transmission case, and increased mortality case that coinfection will increase the R_0 value and that in the reduced growth and poor competitor case that the effect is indeterminate. We also introduced the application of perturbation analysis to coinfection models. Using this method, we showed that we obtain the same trend for the cost of resistance cases when comparing our estimate for the intrinsic growth rate for the coinfection case versus the intrinsic growth rate for the single infection case. We also used this approximation to estimate the percentage of resistance as a function of time. Finally, we analyzed how both the intrinsic growth rate and R_0 respond to a changing treatment rate, compared to the intrinsic growth rate and R_0 value in the single infection case. We found that the change in R_0 and the intrinsic growth rate can be

greater or smaller than the change in the single infection case.

We contend, that this work represents a major contribution toward addressing the question of the effect of multiple infections on the emergence of resistant pathogens. Specifically, we believe that we are the first to perform a full analysis on a multiple infection model with treatment. In addition, we are the first to show that the R_0 for multiple infections can be derived using the Next-Generation Theorem. We contend that we have made a contribution to the literature on deriving R_0 for multiple infections heuristically as our derivation provides much more detail, in particular regarding the role played by propagules. To our knowledge, we are also the first to show that one can estimate the intrinsic rate of growth, by making the biologically relevant assumption that the coinfection efficiency is small as well as provide an estimate for the percent resistance as a function of time.

Clearly, the above investigation has shown that multiple infections play an important role in the emergence of resistant pathogens. Hopefully, it has added awareness from public health perspective, that public health intervention strategies may not only effect the amount of infection but could also effect the amount of coinfection. This in turn could have an unexpected effect on the population dynamics.

Areas of future work could include:

- The development of a disease specific coinfection model, that looks at the various pathways and life stages of a disease.
- A stochastic coinfection model.
- An analysis of various intervention strategies and how they are expected to effect the amount of coinfection.

The author hopes that this work will provide a launching point for further inves-

tigations both mathematical and experimental into the effect of coinfection on the emergence of resistant pathogens.

BIBLIOGRAPHY

[1] S. Alizon and M. van Baalen. Multiple Infections, Immune Dynamics, and the Evolution of Virulence. *American Naturalist*, 172(4), OCT 2008.

[2] H. A. Babiker, L. C. Ranford-Cartwright, and D. Walliker. Genetic structure and dynamics of Plasmodium falciparum infections in the Kilombero region of Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 93(Suppl. 1):S11–S14, FEB 1999.

[3] A. Berman and R.J. Plemmons. *Nonnegative Matrices in the Mathematical Sciences*. Academic Press, 1979.

[4] S. Bonhoeffer, R.E. Lenski, and D. Ebert. The Curse of the Pharaoh: The Evolution of Virulence in Pathogens with Long Living Propagules. *Proceedings: Biological Sciences*, 263(1371):pp. 715–721, 1996.

[5] JC de Roode, R Culleton, A. S. Bell, and A. F. Read. Competitive release of drug resistance following drug treatment of mixed Plasmodium chabaudi infections. *Malaria Journal*, 3, SEP 2004.

[6] O. Diekmann, J.A.P. Heesterbeek, and J.A. Metz. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28:365–382, 1990.

[7] C. R. Braden et a1. Simultaneous Infection with Multiple Strains of Mycobacterium tuberculosis. *Clinical Infectious Diseases*, 33(6):e42, 2001.

[8] H. W. Hethcote. The Mathematics of Infectious Diseases. *Siam Review*, 42(4):pp. 599–653, 2000.

[9] S. Huijben, W. A. Nelson, A. R. Wargo, D. G. Sim, D. R. Drew, and A. F. Read. Chemotherapy,Within-host Ecology and the Fitness of Drug-Resistant Malaria Parasites. *Evolution*, 64:2952–2968, 2010.

[10] A. Hurford, D. Cownden, and T. Day. Next-generation tools for evolutionary invasion analyses. *Journal of the Royal Society Interface*, 7(45):561–571, APR 6 2010.

[11] N. Mideo, S. Alizon, and T. Day. Linking within- and between-host dynamics in the evolutionary epidemiology of infectious diseases. *Trends in Ecology and Evolution*, 23(9):511 – 517, 2008.

[12] J. Mosquera and F. R. Adler. Evolution of Virulence: a Unified Framework for Coinfection and Superinfection. *Journal of Theoretical Biology*, 195(3):293 – 313, 1998.

[13] M. Nowak and R. May. Superinfection and the Evolution of Parasite Virulence. *Proceedings of Biological Sciences*, pages 81–89, 1994.

[14] S. Otto and T. Day. *A Biologists Guide to Mathematical Modeling in Ecology and Evolution*. Princeton University Press, 2007.

[15] P. van den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1-2):29 – 48, 2002.

[16] A. Read and L. Taylor. The Ecology of Genetically Diverse Infections. *Science*, 292(5519):1099–1102, 2001.

[17] O. Restif. Evolutionary epidemiology 20 years on: Challenges and prospects. *Infection Genetics and Evolution*, 9(1):108–123, JAN 2009.

[18] D. Sitki-Green, M. Covington, and N. Raab-Traub. Compartmentalization and Transmission of Multiple Epstein-Barr Virus Strains in Asymptomatic Carriers. *Journal of Viriology*, 77(3):1840–1847, 2003.

[19] B. Sury. The theory of equations and the birth of modern group theory: An Introduction to galois theory. *Resonance*, 4:47–60, OCT 1999.

[20] M. van Baalen and M. W. Sabelis. The Dynamics of Multiple Infection and the Evolution of Virulence. *American Naturalist*, pages 881–910, 1995.

[21] A. Wargo, S. Huijben, J de Roode, J. Shepherd, and A. Read. Competitive release and facilitation of drug-resistant parasites after therapeutic chemotherapy in a rodent malaria model. *Proceedings of the National Academy of Sciences of the United States of America*, 104(50):19914–19919, DEC 11 2007.

[22] World Health Organization. WHO Guidelines for the Treatment of Malaria Second Edition. *http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html*, 2010.

Appendices

0.1 Appendix A

0.2 Application of Next Generation Theorem, Derivation of R_0

Recall that the Jacobian of system 2.4 evaluated at the endemic equilibrium takes on the following form:

$$\begin{pmatrix} J_B & J_1 \\ 0 & J_A \end{pmatrix} \tag{0.1}$$

Since all the eigenvalues of J_B are assumed to have negative real part then we need only to analyze the eigenvalues of J_A in order to analyze the stablity of our system. We notice that we can partition our Matrix J_A into $J_A = F - V$ where

$$J_A = \begin{pmatrix} -\nu + \hat{S}\beta_A - \sigma h_B - \mu_A & \hat{S}\beta_A & \hat{S}\beta_{\mathrm{AB},A} & \hat{S}\beta_{\mathrm{BA},A} & S\beta_{\mathrm{TA}} & \hat{S}\beta_{\mathrm{TA}} & \hat{S}\beta_{\mathrm{TAB},A} & \hat{S}\beta_{\mathrm{TBA},A} \\ 0 & -\nu - \mu_A & 0 & 0 & 0 & 0 & 0 & 0 \\ \sigma\left(\hat{h}_B\right) & 0 & -\nu - \mu_{\mathrm{AB}} & 0 & 0 & 0 & 0 & 0 \\ \sigma\hat{I}_B\beta_A & \sigma\hat{I}_B\beta_A & \sigma\hat{I}_B\beta_{\mathrm{AB},A} & -\nu - \mu_{\mathrm{BA}} + \sigma\hat{I}_B\beta_{\mathrm{BA},A} & \sigma\hat{I}_B\beta_{\mathrm{TA}} & \sigma\hat{I}_B\beta_{\mathrm{TA}} & \sigma\hat{I}_B\beta_{\mathrm{TAB},A} & \sigma\hat{I}_B\beta_{\mathrm{TBA},A} \\ \nu & 0 & 0 & 0 & -\mu_{\mathrm{TA}} & 0 & 0 & 0 \\ 0 & \nu & 0 & 0 & 0 & -\mu_{\mathrm{TA}} & 0 & 0 \\ 0 & 0 & \nu & 0 & 0 & 0 & -\mu_{\mathrm{TAB}} & 0 \\ 0 & 0 & 0 & \nu & 0 & 0 & 0 & -\mu_{\mathrm{TBA}} \end{pmatrix}$$

and

$$F = \begin{pmatrix} \hat{S}\beta_A & \hat{S}\beta_A & \hat{S}\beta_{\mathrm{AB},A} & \hat{S}\beta_{\mathrm{BA},A} & \hat{S}\beta_{\mathrm{TA},A} & \hat{S}\beta_{\mathrm{TA},A} & \hat{S}\beta_{\mathrm{TAB},A} & \hat{S}\beta_{\mathrm{TBA},A} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \sigma\hat{I}_B\beta_A & \sigma\hat{I}_B\beta_A & \sigma\hat{I}_B\beta_{\mathrm{AB},A} & \sigma\hat{I}_B\beta_{\mathrm{BA},A} & \sigma\hat{I}_B\beta_{\mathrm{TA},A} & \sigma\hat{I}_B\beta_{\mathrm{TA},A} & \sigma\hat{I}_B\beta_{\mathrm{TAB},A} & \sigma\hat{I}_B\beta_{\mathrm{TBA},A} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \nu+\mu_A+\sigma h_B & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \nu+\mu_A & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma h_B & 0 & \nu+\mu_{\mathrm{AB}} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \nu+\mu_{\mathrm{BA}} & 0 & 0 & 0 & 0 \\ -\nu & 0 & 0 & 0 & \mu_{\mathrm{TA}} & 0 & 0 & 0 \\ 0 & -\nu & 0 & 0 & 0 & \mu_{\mathrm{TA}} & 0 & 0 \\ 0 & 0 & -\nu & 0 & 0 & 0 & \mu_{\mathrm{TAB}} & 0 \\ 0 & 0 & 0 & -\nu & 0 & 0 & 0 & \mu_{\mathrm{TBA}} \end{pmatrix}.$$

We notice that F is a non-negative matrix and that V is an M-matrix therefore we can apply the Next-Generation Theorem and

$$\begin{aligned} s\left(J_A\right) < 0 \quad &<=> \quad \rho\left(FV^{-1}\right) < 1 \\ s\left(J_A\right) > 0 \quad &<=> \quad \rho\left(FV^{-1}\right) > 1 \\ s\left(J_A\right) = 0 \quad &<=> \quad \rho\left(FV^{-1}\right) = 1 \end{aligned}$$

Taking the spectral radius of FV^{-1} we obtain:

(0.2)

$$\begin{aligned} \rho\left(FV^{-1}\right) = &\frac{\sigma \hat{I}_B \beta_{\mathrm{BA},A}}{\nu + \mu_{\mathrm{BA}}} + \frac{\hat{S}\beta_A}{\nu + \sigma h_B + \mu_A} + \frac{\hat{S}\sigma \hat{h}_B \beta_{\mathrm{AB},A}}{\left(\nu + \mu_{\mathrm{AB}}\right)\left(\nu + \sigma \hat{h}_B + \mu_A\right)} \\ &+ \frac{\hat{S}\nu\beta_{\mathrm{TA},A}}{\mu_{\mathrm{TA}}\left(\nu + \sigma \hat{h}_B + \mu_A\right)} + \frac{\hat{S}\nu\sigma \hat{h}_B \beta_{\mathrm{TAB},A}}{\left(\nu + \mu_{\mathrm{AB}}\right)\mu_{\mathrm{TAB}}\left(\nu + \sigma \hat{h}_B + \mu_A\right)} + \frac{\nu\sigma \hat{I}_B \beta_{\mathrm{TBA},A}}{\left(\nu + \mu_{\mathrm{BA}}\right)\mu_{\mathrm{TBA}}} \end{aligned}$$

We will refer to quantity 0.2 as R_0. Applying the Next-Generation theorem we have that if $R_0 > 1$ then our system is unstable and if $R_0 < 1$ then our system is locally stable.

0.3 Stability Conditions for the Strain B system

Assume the following system of differential equations:

$$\begin{aligned} \dot{S} &= \Theta - \mu S - h_B S \\ \dot{I}_B &= h_B S - \sigma h_B I_B - \mu_B I_B - \nu I_B \\ \dot{I}_{\mathrm{BB}} &= \sigma h_B I_B - \mu_{\mathrm{BB}} I_{\mathrm{BB}} - \nu I_{\mathrm{BB}} \\ \dot{T}_B &= \nu I_B - \mu_{TB} T_B \\ \dot{T}_{\mathrm{BB}} &= \nu I_{\mathrm{BB}} - \mu_{TBB} T_{BB} \end{aligned} \tag{0.3}$$

where

$$h_B = \beta_B I_B + \beta_{\mathrm{BB},B} I_{\mathrm{BB}} + T_B \beta_{\mathrm{TB},B} + T_{\mathrm{BB}} \beta_{\mathrm{TBB},B}$$

If we apply the assumptions II.5 that class I_B and class I_{BB} have the same transmission efficiency and mortality rate, and that class T_B and T_{BB} have the same transmission efficiency and mortality rate we can define new variables $\dot{I}_{B_{new}} = \dot{I}_B + \dot{I}_{BB}$ and $\dot{T}_{B_{new}} = \dot{T}_B + \dot{T}_{BB}$ and rewrite our system as

$$\begin{aligned} \dot{S} &= \Theta - \mu S - h_B S \\ \dot{I}_{B_{new}} &= h_B S - \sigma h_{B_{new}} I_{B_{new}} - \mu_B I_{B_{new}} - \nu I_{B_{new}} \\ \dot{T}_{B_{new}} &= \nu I_{B_{new}} - \mu_{TB} T_{B_{new}} \end{aligned} \tag{0.4}$$

where

$$h_B = \beta_B I_{B_{new}} + T_{B_{new}} \beta_{\mathrm{TB},B} \tag{0.5}$$

This system is identical in form to system 0.9 when single infections only are permitted. Therefore we have that the endemic B equilibrium of our system is stable when $\hat{h}_B > 0$.

0.4 Appendix B

0.5 Derivation of R_0 for Single Infections Only

We derive an expression for R_0 in the single infection case. Consider the following system of differential equations:

$$
\begin{aligned}
\dot{S} &= \Theta - \mu S - h_A S - h_B S \\
\dot{I}_B &= h_B S - \mu_B I_B - \nu I_B \\
\dot{T}_B &= \nu I_B - \mu_{TB} T_B \\
\dot{I}_A &= h_A S - \mu_A I_A - \nu I_A \\
\dot{T}_A &= \nu I_A - \mu_{TA} T_A
\end{aligned} \tag{0.6}
$$

$$
h_A = \beta_A I_A + T_A \beta_{\mathrm{TA},A} \tag{0.7}
$$

$$
h_B = \beta_B I_B + T_B \beta_{\mathrm{TB},B} \tag{0.8}
$$

Where we have used the same notational conventions as before.

If there is no A strain, system 0.6 reduces to the following strain B only system:

$$
\begin{aligned}
\dot{S} &= \Theta - \mu S - h_B S \\
\dot{I}_B &= h_B S - \mu_B I_B - \nu I_B \\
\dot{T}_B &= \nu I_B - \mu_{TB} T_B
\end{aligned} \tag{0.9}
$$

This system had two equilibrium points. The first is the disease free equilibrium where

$$
\begin{aligned}
\hat{T}_B &= 0 \\
\hat{I}_B &= 0 \\
\hat{S} &= \frac{\theta}{\mu}
\end{aligned} \tag{0.10}
$$

and the second is the endemic equilibrium where:

$$
\begin{aligned}
\hat{T}_B &= \frac{\nu h_B}{\nu\beta_{\mathrm{TB}} + \beta_B\mu_{\mathrm{TB}}} \\
\hat{I}_B &= \frac{\mu_{\mathrm{TB}} h_B}{\nu\beta_{\mathrm{TB}} + \beta_B\mu_{\mathrm{TB}}} \\
\hat{S} &= \frac{(\nu + \mu_B)\,\mu_{\mathrm{TB}}}{\nu\beta_{\mathrm{TB}} + \beta_B\mu_{\mathrm{TB}}}.
\end{aligned} \tag{0.11}
$$

Taking the Jacobian of system 0.5 at the endemic equilibrium we obtain:

(0.12)

$$
\begin{pmatrix}
-\mu - \hat{I}_B\beta_B - \hat{T}_B\beta_{\mathrm{TB},B} & -\hat{S}\beta_B & -\hat{S}\beta_{\mathrm{TB},B} & -\hat{S}\beta_A & -\hat{S}\beta_{\mathrm{TA},A} \\
\hat{I}_B\beta_B + \hat{T}_B\beta_{\mathrm{TB},B} & -\nu + \hat{S}\beta_B - \mu_B & \hat{S}\beta_{\mathrm{TB},B} & 0 & 0 \\
0 & \nu & -\mu_{\mathrm{TB}} & 0 & 0 \\
0 & 0 & 0 & -\nu + \hat{S}\beta_A - \mu_A & \hat{S}\beta_{\mathrm{TA},A} \\
0 & 0 & 0 & \nu & -\mu_{\mathrm{TA}}
\end{pmatrix}
$$

which has the following block-triangular form:

$$
\begin{pmatrix}
J_B & F \\
0 & J_A
\end{pmatrix} \tag{0.13}
$$

Where

$$
J_B = \begin{pmatrix}
-\mu - \hat{I}_B\beta_B - \hat{T}_B\beta_{\mathrm{TB}} & -\hat{S}\beta_B & -\hat{S}\beta_{\mathrm{TB}} \\
\hat{I}_B\beta_B + \hat{T}_B\beta_{\mathrm{TB}} & -\nu + \hat{S}\beta_B - \mu_B & \hat{S}\beta_{\mathrm{TB}} \\
0 & \nu & -\mu_{\mathrm{TB}}
\end{pmatrix} \tag{0.14}
$$

is the Jacobian of system 0.9 and

$$J_A = \begin{pmatrix} -\nu + S\beta_A - \mu_A & S\beta_{\mathrm{TA},A} \\ \nu & -\mu_{\mathrm{TA}} \end{pmatrix} \tag{0.15}$$

is the Jacobian associated with the I_A and T_A differential equations in system 0.6.

Because our starting Jacobian is block triangular, the eigenvalues of system 0.6 are simply the eigenvalues of J_B and J_A. If we examine Jacobian J_B we notice that we cannot obtain an algebraic expression for the eigenvalues. However we can determine the stability of the eigenvalues by applying the Routh-Hurwitz conditions:

Theorem .1. *Routh-Hurwitz Conditions for Local Stability of 3X3 Matrices [14] Given a 3X3 Jacobian matrix we can write the characteristic equation in the following form* $r^3 + a_1 r^2 + a_2 r + a_3 = 0$. *If* $a_1 > 0$, $a_3 > 0$ *and* $a_1 a_2 > a_3$ *then the equilibrium is locally stable.*

Taking the characteristic equation of system 0.9 at the endemic equilibrium we obtain the following conditions for local stablity of the endemic equilibrium.

a) $a_1 > 0 \Leftrightarrow \frac{\Theta\nu^2\beta_{\mathrm{TB}}^2+\beta_B\mu_{\mathrm{TB}}^2(\Theta\beta_B+(\nu+\mu_B)\mu_{\mathrm{TB}})+\nu\beta_{\mathrm{TB}}\mu_{\mathrm{TB}}(2\Theta\beta_B+(\nu+\mu_B)(\nu+\mu_B+\mu_{\mathrm{TB}}))}{(\nu+\mu_B)\mu_{\mathrm{TB}}(\nu\beta_{\mathrm{TB}}+\beta_B\mu_{\mathrm{TB}})} > 0$ This condition is always satisfied since all parameters take on positive values.

b) $a_3 > 0 \Leftrightarrow \Theta\nu\beta_{\mathrm{TB}} > \left(-\Theta\beta_B + \mu\left(\nu + \mu_B\right)\right)\mu_{\mathrm{TB}}$

This condition is equivalent to $\hat{h}_B > 0$.

c) $a_1a_2 > a_3 \Leftrightarrow \frac{\left(\beta_B\mu_{\mathrm{TB}}\left(\mu+\hat{h}_{\mathrm{B}}+\mu_{\mathrm{TB}}\right)+\nu\beta_{\mathrm{TB}}\left(\mu+\nu+\hat{h}_{\mathrm{B}}+\mu_B+\mu_{\mathrm{TB}}\right)\right)\left(\nu\left(\mu+\hat{h}_{\mathrm{B}}\right)\beta_{\mathrm{TB}}(\nu+\mu_B+\mu_{\mathrm{TB}})+\beta_B\mu_{\mathrm{TB}}\left(\mu\mu_{\mathrm{TB}}+\hat{h}_{\mathrm{B}}(\nu+\mu_B+\mu_{\mathrm{TB}})\right)\right)}{(\nu\beta_{\mathrm{TB}}+\beta_B\mu_{\mathrm{TB}})^2} > \hat{h}_{\mathrm{B}}\left(\nu + \mu_B\right)\mu_{\mathrm{TB}}$

Which is satisfied if the force of infection is positive and if all parameters are positive.

We therefore have that if $\hat{h}_B$ is greater than zero then all the eigenvalues of J_B are less than zero. Now all that remains to determine the stability of our system is to evaluate the stability of J_A.

In order to do this we make use of the Next Generation Theorem II.4

We partition our Jacobian into $J_A = F - V$ where

$$F = \begin{pmatrix} S\beta_A & S\beta_{\mathrm{TA},A} \\ 0 & 0 \end{pmatrix} \tag{0.16}$$

and

$$V = \begin{pmatrix} \nu + \mu_A & 0 \\ -\nu & \mu_{\mathrm{TA}} \end{pmatrix}. \tag{0.17}$$

We notice that F represents the entry of new A infections into the system and that V represents the transitions of A infections through the various classes. Therefore $\rho\left(FV^{-}1\right)$ will have the interpretation of the number of secondary infections produced by an infectious A individual. Since F is non-negative and V is an M-matrix, we can apply the Next Generation Theorem and $\rho\left(FV^{-}1\right)$ will completely determine the stability of our system, where $\rho\left(FV^{-}1\right)$ is given by equation 0.18. This also has the biological interpretation of R_0 the number of secondary infections produced by an A individual.

$$\rho\left(FV^{-1}\right) = \frac{\hat{S}\left(\beta_A \mu_{\mathrm{TA}} + \nu\beta_{\mathrm{TA},A}\right)}{\left(\nu + \mu_A\right)\mu_{\mathrm{TA}}} \tag{0.18}$$