MODELLING VIRUS EVOLUTION IN AGE-STRUCTURED POPULATIONS

It is known that COVID-19 has varying infectivity and severity among age groups, yet little is known as to how this may shape viral evolution. Evolutionary models that look a the trade-off between infectivity and lethality will often show the selection of strains with intermediate levels of virulence. It is important to question whether this prediction holds when the viral transmission in younger age groups are taken into consideration due to the greater asymptomatic transmission.

Contrary to standard beliefs, selection in the long run rarely favours strains that maximise their epidemiological basic reproduction ratio, $\mathscr{R}_0$, which is the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection.

It is key to try and integrate pathogen diversity into epidemiological models. This allows us to simulate strain dynamics and acknowledge the evolution of viral strains depending on their infectivity, lethality and cross-immunity.

This highlights the implications underlying the fact that initial infection by a pathogen strain may impact the susceptibility of the host to subsequent infections by new strains brought about from simple mutations . This is due to cross-immunity from the natural immunity of strain 1. An analogous idea looks at the immunity to multiple strains from acquired immunity of a single vaccine. It is clear that COVID is known for its ability to quickly mutate and develop variants, yet will the varied epidemiological properties from these mutations impact the effectiveness of the vaccine.

Consideration of population age-structure is key in understanding the effect of infection in high-risk population groups and intergenerational contact to highlight areas with critical care forecasting. This further necessitates understanding the development of ever changing policy measures. While schools may be flagged as a major source of viral spread, closures in this area could have worse consequences of intergenerational contact, especially if grandparents become the default carers.

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1st September 2021

PROPOSITION

The proposed project will look to adapt existing epidemic models of COVID-19 in age-structured populations to incorporate relationships between competing strains with different levels of infectivity and lethality. A prediction made on these interactions will help predict their relative fitness in different epidemiological contexts.

In doing so, we consider different modelling assumptions, parameter values and compartment interactions. We focus on modelling the host population and ignore the population dynamics of the pathogen, looking at compartmentalised model for infectious disease.

DESCRIPTION OF THE MODELS

Our models are derived from the simple susceptible–infectious– recovered framework (SIR), in which the host population is split into compartments that correspond to the stages in the infectious cycle.

β is the rate of transmission between a susceptible and infected individual.

γ is the rate of recovery, with the average duration of infection being 1/γ.

N is the population size.

b is the brith rate with all newborns initially susceptible to infection.

δ is the natural death rate.

τ is the decreased rate of transmission factor for hospitalised individuals.

ξ is the rate of hospitalisations of infected individuals.

η is the recovery rate of hospitalised individuals.

α is the ageing factor between juveniles and adults which corresponds to an average age at adulthood of $\frac{1}{\alpha}$.

ν is the vaccination rate for susceptible individuals and is used to represent the proportion of susceptible individual vaccinated per unit time.

p is the proportion individuals who get vaccinated "at birth" with imperfect vaccination.

$\phi \in [0,1]$ is the intensity of cross-immunity with individuals susceptible to secondary infection by a different strain with reduced probability by a factor $(1-\phi)$.

σ is the constant rate of loss of acquired immunity back to the susceptible state.

μ is the birth and death rates with all newborns initially susceptible to infection.

Infection occurs through random contacts between susceptible (S) and infected (I) individuals making the rate of infection modelled by $\frac{\beta SI}{N}$.

Throughout this project, we will be using the proportion of individuals and therefore will set $N = 1$, with our notion of density as a continuous representation for population size.

We assume that there is no 'latent stage' of infection. This means that upon contact with the pathogen, the individual goes straight from the susceptible compartment to the infected compartment.

BASIC REPRODUCTIVE RATIO

One of the key concepts in understanding epidemics is the basic reproductive ratio ($\mathscr{R}_0$). It is the epidemiological measure of parasite fitness, though its value is rarely measured directly, with modelled values dependent on the model structures and assumptions. This epidemiological metric is used to describe the transmissibility of an infectious disease and is the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection.

This assumption of a fully susceptible population usually isn't true. For the case with a new virus, making the calculations to determine $\mathscr{R}_0$ at the initial stage was a very crucial tool for epidemiologists in order to predict the epidemic growth when we had few individuals immune. As the pandemic progresses, one may consider the effective reproductive ratio which is calculated instead by considering how some people have gained immunity due to vaccination or having survived infection, by looking at a population made up of both susceptible and non-susceptible hosts.

For an epidemic to occur in a susceptible population we must have the value of $\mathscr{R}_0 > 1$. The expression for the basic reproductive ratio can be formed by intuition, computed as a ratio of known rates over time. We can instead deduce the value of $\mathscr{R}_0$ from initial data, or the expression for $\mathscr{R}_0$ by the next generation matrix (NGM) method.

The next generation matrix is a matrix relating the numbers of newly infected individuals in each category in consecutive generations. We can view this in complete analogy to demographic generations by considering the infection process in terms of consecutive generations of infected individuals.

The growth factor per generation indicates the potential for growth and therefore can be used as the mathematical characterisation of $\mathscr{R}_0$.

To calculate the expression for the basic reproductive ratio from our system of differential equations, we need to find the dominant eigenvalue of the matrix $K = -T\Sigma^{-1}$.

The elements of the NGM (K_{ij}) represent epidemiologically the expected number or proportion of new cases with state-at-infection *i* generated by an individual with state-at-infection *j*.

We define two new matrices:

- **Transmission matrix (T)** describes the production of new infections
- **Transition matrix (Σ)** describes changes in compartment state

We consider only the infected subsystem -the equations that describe the production of new infections and changes in states among infected individuals - to calculate T and Σ .

On the other hand, sometimes we are able to calculate an approximation for $\mathscr{R}_0$ from the initial growth rate of infections. For this method we make a small time approximation whereby the number of susceptible individuals are almost equal to the total number of individuals in the population with few infected individuals to get an first order differential approximation for the rate of change of infections to solve. An approximate vale for $\mathscr{R}_0$ can be calculated upon finding the initial growth rate '*r*' of infections from the medical data.

SIMPLEST SIR MODEL (NO BIRTH/DEATH)

In this model we start with the whole population of healthy cells and one cancerous, mutated cell. An individual cell is chosen to die uniformly at random.

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

By analysis of the S and I nullclines we obtain the axis $I = 0$ being a stationary state for any value of S, with stability for $S < \frac{\gamma}{\beta}$.

The epidemic peak is reached when $\frac{dI}{dt} = 0$ which occurs at $S_{max} = \frac{\gamma}{\beta}$. For this model we can calculate the basic reproductive ratio to be given by $\mathscr{R}_0 = \frac{\beta}{\gamma}$.

$$S_{max} = \frac{1}{\mathscr{R}_0}$$

$$I_{max} = S_0 + I_0 + \frac{\gamma}{\beta}\left[ln\left(\frac{\gamma}{\beta S_0}\right) - 1\right]$$

(see Appendix A for calculation)

Figure 1. shows how the distribution of number of infective individuals in the population changes upon the parameter β. In this model we take the average infection rate to be 7 days which translates into the parameter $\gamma = \frac{1}{52}$.

It is clear that the smallest epidemic peaks occur for lower transmission rates, yet we can also deduce that a slight reduction in β at the beginning of the pandemic (when transmission rate is high) will yield a more prevalent drop in infections compared to that of smaller

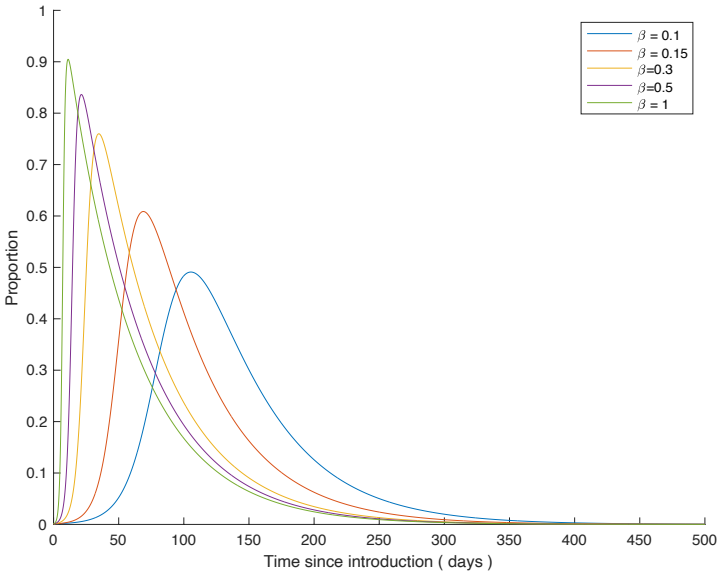


Figure 1.
Basic SIR model of infective individuals with varying β
$\gamma = \frac{1}{52}, I_0 = 0.001, S_0 = 0.999, R_0 = 0$

β values. This highlights the importance of initial implementation of strict government measures.

When considering small time, we can make the approximation of $S \approx N$. This gives use an approximation for the initial growth rate of infections as

$$\frac{dI}{dt} = (\beta N - \gamma) I = (\mathscr{R}_0 - 1)\gamma I.$$

Initially our infections grow exponentially with a growth rate of $(\mathscr{R}_0 - 1)\gamma$. If we can measure the initial growth rates during an epidemic to be 'r' then we can generate an approximation for the basic reproduction ratio to be $\mathscr{R}_0 \approx 1 + \frac{r}{\gamma}$.

SIR MODEL WITH NATURAL BIRTH/DEATH)

A simple development of our previous model introduces birth rates and natural death rates. This is an important factor when looking at long-term models for epidemiological spread or upon placing more focus on the elderly population with a much larger death rate.

$$\frac{dS}{dt} = bN - \beta SI - \delta S$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \delta I$$

$$\frac{dR}{dt} = \gamma I - \delta R$$

We assume that the birth and death rates are identical with $\delta = b = \mu$ ensuring constant population size throughout.

For this model we can calculate the basic reproductive ratio to be given by $\mathcal{R}_0 = \frac{\beta}{\gamma + \mu}$ and by looking at stability of stationary states we obtain the endemic equilibrium,

$$S^* = \frac{1}{\mathcal{R}_0}$$

$$I^* = \frac{\mu}{\beta}(\mathcal{R}_0 - 1)$$

$$R^* = \frac{\gamma}{\beta}(\mathcal{R}_0 - 1)$$

(see Appendix A for calculation)

If $\mathcal{R}_0 < 1$, then there is a disease-free equilibrium which is asymptotically stable and the viral strain dies out. If $\mathcal{R}_0 > 1$, then there is a unique endemic equilibrium which is asymptotically stable, and the infective strain persists within the population.

HOSPITALISATION MODEL

Hospitalisation rates could affect the spread of an infection within the population, with particular influence for that of the older generation.

Let ξ be the rate of hospitalisations and η be the recovery rate for those hospitalised. We also presume that the rate of transmission decreases by a factor of τ for hospitalised individuals due to the increased levels of PPE.

We again are not looking at the virulence of infection, with a greater focus on how changing parameters affect infections.

$$\frac{dS}{dt} = -\beta S(I + \tau H)$$

$$\frac{dI}{dt} = \beta S(I + \tau H) - (\gamma + \xi)I$$

$$\frac{dH}{dt} = \xi I - \eta H$$

$$\frac{dR}{dt} = \gamma I + \eta H$$

For this model we can calculate the basic reproductive ratio via the next generation matrix method.

$$\mathcal{R}_0 = \frac{\beta}{\gamma + \xi} \cdot \left(1 + \frac{\tau \xi}{\eta}\right)$$

(see Appendix A for T and Σ)

This is a decreasing function in ξ for $\eta > \tau\gamma$ with Figure 2. showing how the value of $\mathcal{R}_0$ varies as a function of ξ.

It is important to note that to evaluate the effect of hospitalisations on the spread of COVID, we would have to include many more parameters including the increased death rate for hospitalised patients.

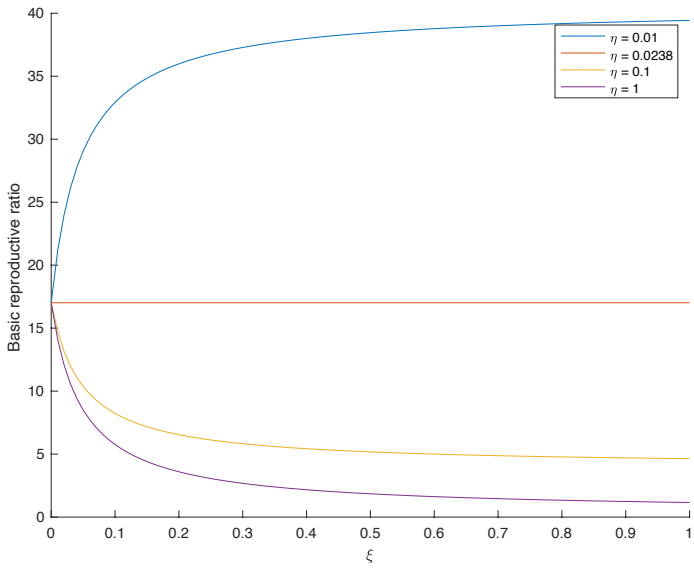


Figure 2.
How the value of $\mathcal{R}_0$ varies with ξ for different η
$\gamma = 0.0476, \tau = 0.5, \beta = 0.81$

VACCINATION

There are two ways to represent the introduction of vaccination in our epidemic model. We will start considering vaccination introduced with a vaccination rate ν for the susceptible population, representing the proportion of susceptible individual vaccinated per unit of time. We make the assumptions that immunisation is immediate and provides life-long protection.

$$\frac{dS}{dt} = bN - \beta SI - (\delta + \nu)S$$

$$\frac{dI}{dt} = \beta SI - (\gamma + \delta)I$$

$$\frac{dR}{dt} = \gamma I - \delta R + \nu S$$

This model takes the vaccinated proportion of the population and considers them as recovered individuals, yet can be used to generalise vaccination programmes that are not carried out at birth.

An alternative model develops this by introducing compartments for susceptible and infected vaccinated individuals with a constant proportion p of the population vaccinated.

$$\frac{dS_N}{dt} = bN(1-p) - (\delta + \beta_{NN}I_N + \beta_{VN}I_V)S_N$$

$$\frac{dS_V}{dt} = bNp - (\delta + \beta_{NV}I_N + \beta_{VV}I_V)S_V$$

$$\frac{dI_N}{dt} = (\beta_{NN}I_N + \beta_{VN}I_V)S_N - (\alpha_N + \gamma_N + \delta)I_N$$

$$\frac{dI_V}{dt} = (\beta_{NV}I_N + \beta_{VV}I_V)S_V - (\alpha_V + \gamma_V + \delta)I_V$$

$$\frac{dR}{dt} = \gamma_N I_N + \gamma_V I_V - \delta R$$

Despite the second model involving vaccination at birth, which is a reasonable approximation for several infant immunisation programmes, this is not relevant for COVID. However, we can incorporate this model when looking at vaccination in age-structured populations by have vaccination “at birth” for the adult population.

It is also important to note that in the second model we assume imperfect vaccination. This means that vaccinated individuals can be infected and can then infect others; however, infection confers full immunity irrespective of vaccination status.

From the second model, we will be able to calculate the critical vaccination coverage that result in an effective reproduction ratio of one.

The basic reproductive ratio is displayed in Appendix A along with T and Σ from the next generation matrix method.

It can be noted that the expression for $\mathcal{R}_0$ is the weighted sum of the basic reproduction ratio in unvaccinated and vaccinated host populations if $\beta_{NN} = \beta_{NV}$ and $\beta_{VV} = \beta_{VN}$ or $\beta_{NN} = \beta_{VN}$ and $\beta_{VV} = \beta_{NV}$.

By assuming this, we can derive the critical vaccination coverage to be $p_c = 1 - \frac{1 - \mathcal{R}_0^V}{\mathcal{R}_0^N - \mathcal{R}_0^V}$ with $\mathcal{R}_0^N = \frac{\beta_{NN}\, b}{n\delta}$ and $\mathcal{R}_0^V = \frac{\beta_{VV}\, b}{\nu\delta}$.

A trivial equilibrium is the disease-free equilibrium listed in Appendix A, yet we look at the cases where $\mathcal{R}_0 > 1$ prior to vaccination, meaning that the virus will spread and reach an endemic equilibrium.

$$S_N^* = \frac{N}{\mathcal{R}_0} \cdot \frac{b}{\delta}$$

$$I_N^* = \frac{\delta}{\beta_{NN}} (\mathcal{R}_0 - 1)$$

$$R^* = \frac{\gamma_N}{\beta_{NN}} (\mathcal{R}_0 - 1)$$

Upon introduction of a vaccine, if $p < p_c$ then we will obtain a new endemic equilibrium with lower disease incidence with $p > p_c$ leading to the virus being driven to extinction.

SECONDARY INFECTION AND CROSS-IMMUNITY

We now consider a double-strain model whereby following primary infection by one strain and recovery, individuals are susceptible to secondary infection by the other strain with a probability reduced by a factor $(1-\phi)$.

This model can be interpreted for two different scenarios; re-infection by the same strain or re-infection by a new mutated strain. We allow for loss of acquired immunity back to the susceptible state at a constant rate σ and make the assumption that this loss is the same for all infections.

Analysis of different strains of COVID would allow us to hypothesis whether this assumption is true and whether we should set the loss of natural immunity from mutated strains to be will be less upon new infection. One should note that a further development involves the addition of vaccination to our model, whereby the loss of vaccinated immunity may be differ from that of natural immunity.

Initially, when the number of recovered individuals with natural immunity is people is negligible, the favoured viral strains are those transmitted more efficiently. Yet the proportion of the population with natural immunity increases, there is increased benefits from viral strains infecting the same patient twice. We can hypothesise that these variants may also evade vaccine-induced immunity, making them a concern to the vaccine programmes initiated.

Upon high roll-out of the COVID vaccine, our attention should shift to variants that have the ability to evade vaccinated individuals to retain its fitness and pathogenicity. This would be a major problem, as such a variant would limit the benefits of the immunisation programme on infection rates, but rather focus on reduced virulence.

$$\frac{dS}{dt} = \mu - (\Lambda_1 + \Lambda_2 + \mu)S + \sigma(R_1 + R_2 + R_{12})$$

$$\frac{dI_1}{dt} = \Lambda_1 S - (\mu + \gamma_1)I_1$$

$$\frac{dI_2}{dt} = \Lambda_2 S - (\mu + \gamma_2)I_2$$

$$\frac{dI_{12}}{dt} = (1-\phi)\Lambda_2 R_1 - (\mu + \gamma_2)I_{12}$$

$$\frac{dI_{21}}{dt} = (1-\phi)\Lambda_1 R_2 - (\mu + \gamma_1)I_{21}$$

$$\frac{dR_1}{dt} = \gamma_1 I_1 - [(1-\phi)\Lambda_2 + \sigma + \mu]R_1$$

$$\frac{dR_2}{dt} = \gamma_2 I_2 - [(1-\phi)\Lambda_1 + \sigma + \mu]R_2$$

$$\frac{dR_{12}}{dt} = \gamma_1 I_{21} + \gamma_2 I_{12} - (\sigma + \mu)R_{12}$$

We have the Λ_i represents the force of infection of strain i with $\Lambda_1 = \beta_1(I_1 + I_{21})$ and $\Lambda_2 = \beta_2(I_2 + I_{12})$.

We will model our two strain problem by introducing strain 2 with a very low prevalence once strain 1 has reached endemic equilibrium,. This mimics a viral mutation and allows us to predict whether a new mutated strain with specified parameters will reach an endemic equilibrium in the population by either replacing strain 1 or by coexistence.

If either strain has a much lower basic reproductive ratio than its competitor, its prevalence in the population asymptotically approaches zero.

From the single strain model we previously encountered, we can deduce the endemic equilibrium for strain 1.

$$S^* = \frac{\gamma_1 + \mu}{\beta_1}$$

$$I_1^* = \frac{\mu + \sigma}{\gamma_1 + \mu + \sigma}\left(1 - \frac{\gamma_1 + \mu}{\beta_1}\right)$$

$$R_1^* = \frac{\gamma_1}{\gamma_1 + \mu + \sigma}\left(1 - \frac{\gamma_1 + \mu}{\beta_1}\right)$$

We must note that this endemic equilibrium achieved will be stable if the systems basic reproductive ratio is greater than 1 ($\mathcal{R}_0 = \frac{\beta_1}{\gamma_1 + \mu} > 1$).

Since the value of $\mathcal{R}_0$ doesn't depend on σ (the rate of loss of acquired immunity) then we can see that the proportion of individuals recovered is larger for longer immune period $1/\sigma$.

We can approximate the initial infection rate from the strain 2 with $S \approx S^* = \frac{1}{\mathcal{R}_0}$ to obtain an initial growth rate.

$$r = \beta_2 \left[\frac{1}{{}^1\mathcal{R}_0} - \frac{1}{{}^2\mathcal{R}_0} + \frac{\gamma_1}{\gamma_1 + \mu + \sigma}(1-\phi)(1 - \frac{1}{{}^1\mathcal{R}_0}) \right]$$

(See Appendix A for calculation)

We can compare two different strains with the same basic reproductive ratio (${}^1\mathcal{R}_0 = {}^2\mathcal{R}_0$) but different infectivity and transmission rate. The initial growth rate can therefore be approximated to be,

$$r = (\gamma_2 + \mu)(1-\phi)\frac{\gamma_1}{\gamma_1 + \mu + \sigma}(\mathcal{R}_0 - 1)$$

We can compare this initial infection rate directly to the case with only a single strain where $r = (\mathcal{R}_0 - 1)(\gamma_2 + \mu)$, showing that a secondary infection will have a reduced infection rate of by the fraction $(1-\phi)\frac{\gamma_1}{\gamma_1 + \mu + \sigma}$.

Figure 3. displays how the initial rate of infection of strain 2 varies depending on whether there is previous immunity from a previous strain.

There are four cases to consider when we have a new invading strain:

- Both strains leave the population

Due to the fact that we have a model with constant population size, we have neither strain remaining in the population if the susceptible population has $S = 1$. If an endemic equilibrium with strain 1 occurs then it is impossible for the strain to leave the population unless it is

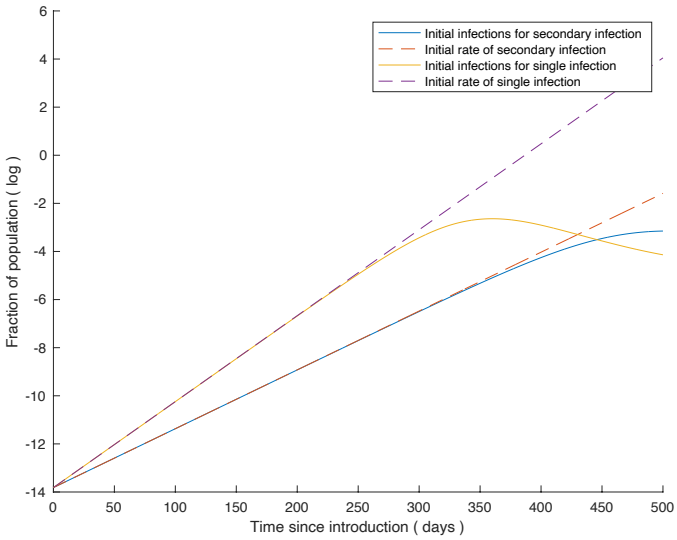


Figure 3.
$\mu = 0.000055, \sigma = 0.00476, \phi = 0.2, \mathcal{R}_0 = 1.5$
$\gamma_1 = 0.0286, \gamma_2 = 0.0714$

replaced by a new invading strain. This case is stable if and only if both strains have a basic reproductive rate greater than 1.

- Strain 1 endemic

We have already deduced the equations for the endemic equilibrium with strain 1, with stability determined by the rate of invasion of strain 2. We must have that ${}^1\mathcal{R}_0 > 1$ and $r < 0$.

- Strain 2 endemic

This is the symmetric of the case with strain 1 and will occur when the growth rate of strain 2 is greater than zero due to the constant population size.

We will take ${}^1\mathcal{R}_0 = 2$ and using our equation for r determine that the limiting value is ${}^2\mathcal{R}_0 = 1.187$, so in order for strain 2 to not replace strain 1 upon invasion or coexist with strain 1, we must have ${}^2\mathcal{R}_0 < 1.187$.

- Coexistence

If $\phi = 1$, then coexistence is only possible when ${}^1\mathcal{R}_0 = {}^2\mathcal{R}_0$, with a novel strain unable to spread if introduced at a very low density against an endemic strain.

An example of this is given in Figure 4. where ${}^2\mathcal{R}_0 = 1.4$ which is above the limiting value of r meaning that

strain 2 will become present in the population, and Figure 5. where $\mathscr{R}_0^2 = 1.17$ which is below the limiting value. Note that the rate of invasion significantly different for only small variations in the ${}^2\mathscr{R}_0$ value.

This is an example of invasion analysis, however, it is possible to determine whether growth will lead to replacement or coexistence for $\phi \neq 1$ from stability analysis of the Jacobian matrix and corresponding eigenvalues (not done in this project). In which case numerical simulated solutions are best used to determine this.

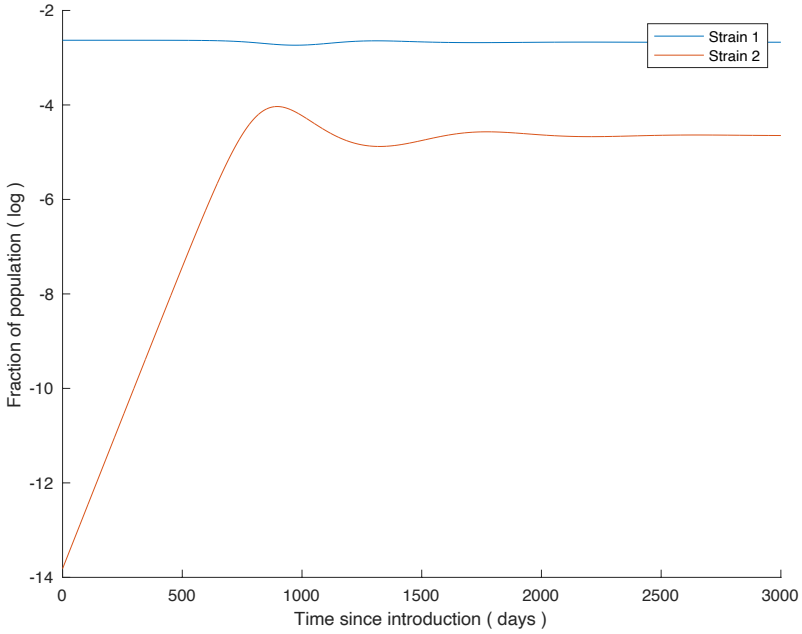


Figure 4.
$\mu = 0.000055\,, \sigma = 0.00476\,, \phi = 0.2\,, \mathscr{R}_0^1 = 2\,, \mathscr{R}_0^2 = 1.4$
$\gamma_1 = 0.0286\,, \gamma_2 = 0.0714$

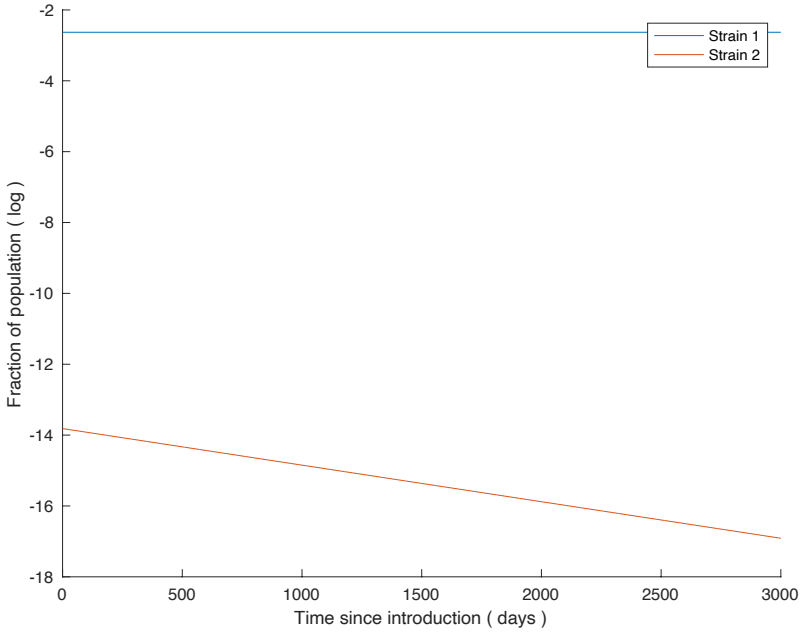
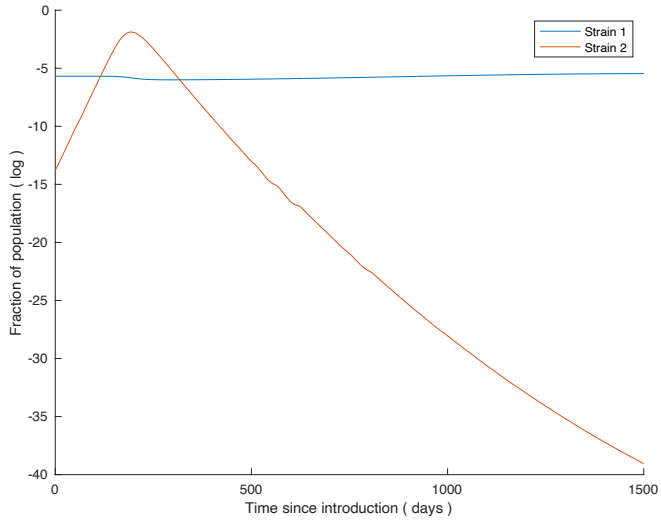
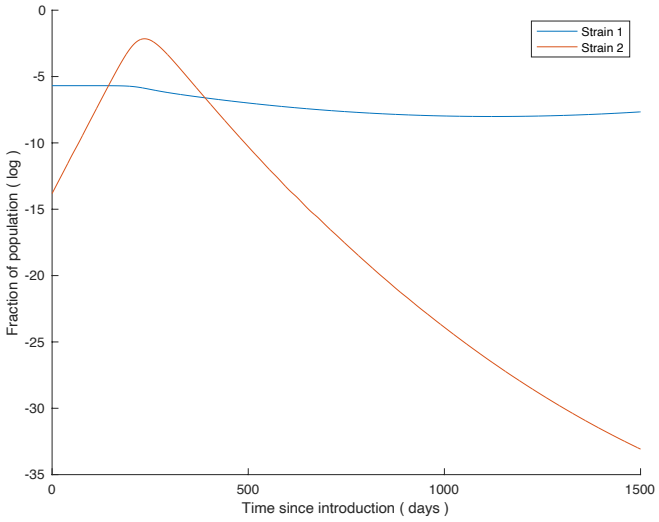


Figure 5.
$\mu = 0.000055\,, \sigma = 0.00476\,, \phi = 0.2\,, \mathscr{R}_0^1 = 2\,, \mathscr{R}_0^2 = 1.7$
$\gamma_1 = 0.0286\,, \gamma_2 = 0.0714$

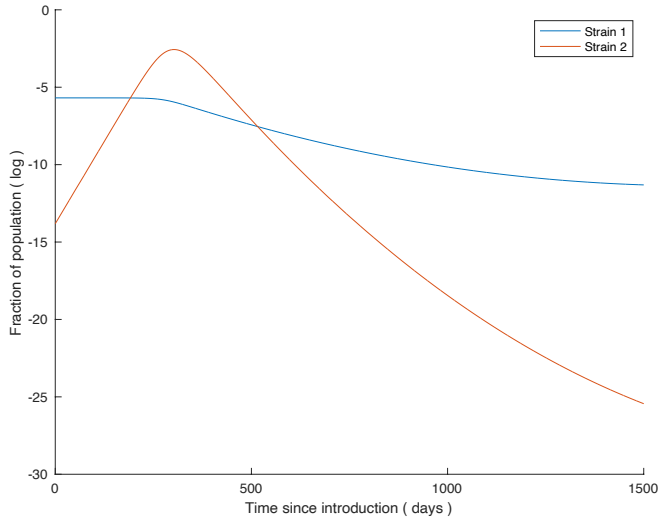
Figure 6. Shows a series of graphs of the resulting infection strain for varying intensity of cross-immunity with strain 1 having parameters $\mu = 0.000055, \sigma = 0.00014, \gamma = 0.0286, \beta = 0.05731$ and strain 2 having parameters $\mu = 0.000055, \sigma = 0.00014, \gamma = 0.0714, \beta = 0.14291$. As ϕ increases, we can see that the maximum infections decreases, peaking at a later time, and the number of remaining strain 1 infections decreases.



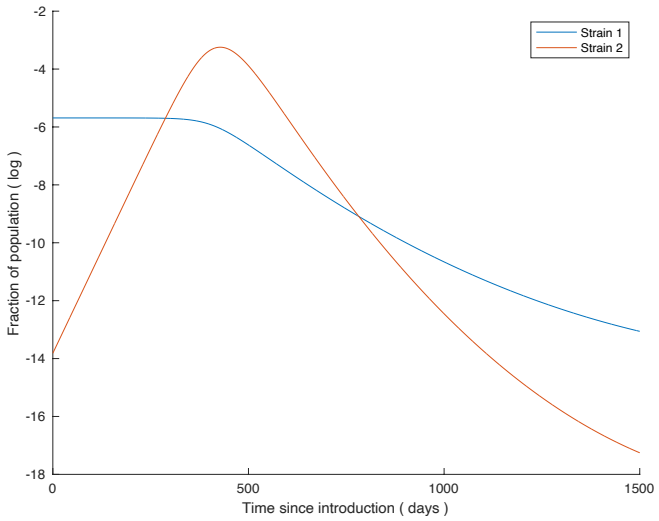
$\phi = 0$



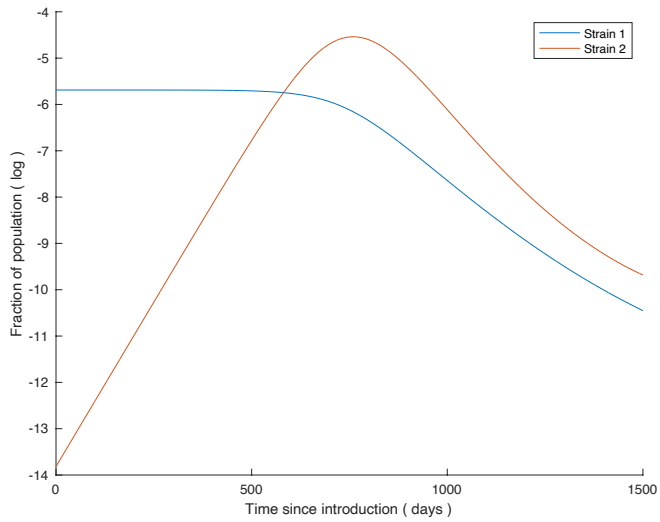
$\phi = 0.2$



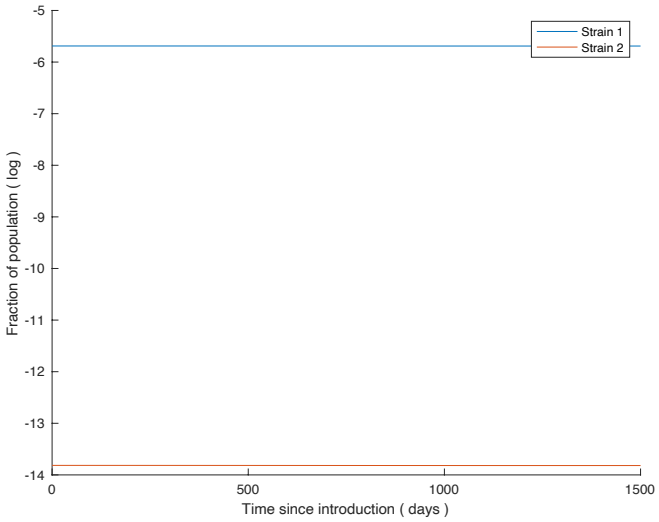
$\phi = 0.4$



$\phi = 0.6$



$\phi = 0.8$



$\phi = 1$

Figure 6.

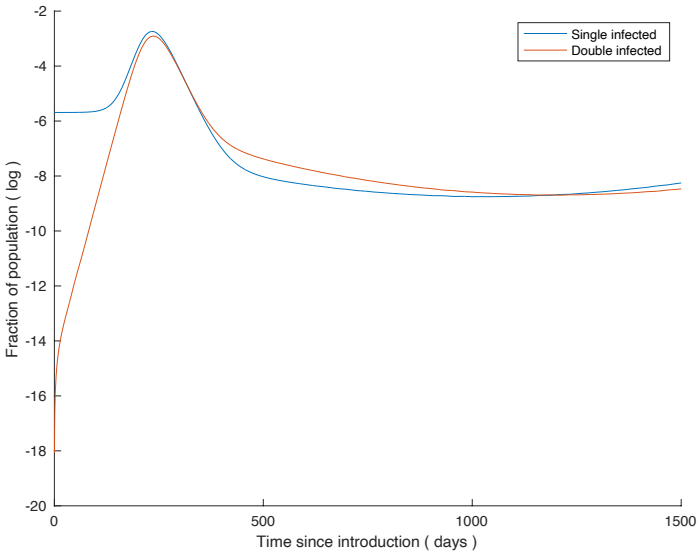


Figure 7.
$\phi = 0.2$

For the same values we can also model the change in single and double infections shown in Figure 7. where we see a peak in both infections simultaneously.

AGE-STRUCTURED POPULATION MODEL

We can develop this SIR model further by introducing two age groups (juveniles and adults) with varying death rates, rates of recovery and ageing factor.

$$\frac{dSJ}{dt} = bA - \beta(I_J + I_A)SJ - \alpha SJ - \delta_J SJ$$

$$\frac{dSA}{dt} = \alpha SJ - \beta(I_J + I_A)SA - \delta_A SA$$

$$\frac{dI_J}{dt} = \beta(I_J + I_A)SJ - (\alpha + \delta_J + \gamma_J)I_J$$

$$\frac{dI_A}{dt} = \beta(I_J + I_A)SA - (\delta_A + \gamma_A)I_A + \alpha I_J$$

$$\frac{dR_J}{dt} = \gamma_J I_J - (\alpha - \delta_J)R_J$$

$$\frac{dR_A}{dt} = \gamma_A I_A + \alpha R_J - \delta_A R_A$$

We are assuming equal transmission rates, and therefore equal contact rates, within and between age groups by considering only a single parameter β for the rate of transmission between all susceptible and infected individuals.

The following box-and-arrow diagram depicts the epidemic spread in this model.

For this model we can calculate the basic reproductive ratio using the next generation matrix method.

$$\mathscr{R}_0 = \frac{\beta N_A(\alpha + \delta_J + \gamma_J) + \beta N_J(\alpha + \delta_A + \gamma_A)}{(\alpha + \delta_J + \gamma_J)(\delta_A + \gamma_A)}$$

(see Appendix A for T and Σ)

Upon developing our model to next incorporate three age structures within the population (juveniles, adults and seniors), it would become apparent that the adult age generation has great importance for mitigating transmission due to being the “sandwich” generation, caring for both the elderly and infants.

Upon modelling this demographic, we would expect to have increased transmission parameter between juveniles/adults and seniors/adults, with an almost negligible transmission parameter between juveniles/seniors.

In order to combat this increased risk of susceptibility of infection, the government implemented policies and industry emergency policy measures to counter family economic crises in this situation. This was particularly prevalent for vulnerable workers and those with unpredictable job outcomes, who are less able to comply with policies that allow social distancing.

AGE-STRUCTURED MODEL WITH TWO STRAINS

The differential equations that describe this model are written in Appendix A.

Note that in this model we have thought of the transmission rate and rate of recovery to vary between the Juvenile and Adult populations but the rate of loss of immunity to be independent of age.

We cannot assume the birth rate to equal the death rates for a constant population size as before due to the introduction of two age groups. Instead we can either consider constant N with A and J varying, or constant N with A and J of constant size.

Our focus will be on a model with constant proportions of Juveniles and Adults in the population.

$$\frac{dJ}{dt} = \mu A - (\delta_J + \alpha)J = 0$$

$$\frac{dA}{dt} = \alpha J - \delta_A A = 0$$

An example would be when we have a 1:1 ratio of Juveniles and Adults in the population leading to $\alpha = \delta_A$ and $\mu = \delta_J + \delta_A$.

Our next model will assume that $\gamma_J = 0.07$ and $\gamma_A = 0.02$, with equal transmission rates for both age groups determined by the basic reproductive ratio $^1\mathcal{R}_0 = 2$. Again we will introduce our new strain variant once we have reached endemic equilibrium to compare how the proportion of each age group effects the endemic progression.

Figure 8. is a table of values at endemic equilibrium of strain 1 in each age group before introducing strain 2. It is the proportion of susceptible individuals in each age category at endemic equilibrium of strain 1 which determines the optimal viral mutation. A 1:3 ratio infected by strain 1 will lead to a large proportion of susceptible juveniles, meaning that a mutation favouring this age group would be most probable to become present at equilibrium in the population.

Ratio A:J	1:3	1:1	3:1
S_J^*	0.415256	0.272085	0.102176
S_A^*	0.138223	0.270537	0.288893
I_J^*	0.028215	0.010268	0.008446
I_A^*	0.013386	0.019852	0.076542
R_J^*	0.306534	0.217652	0.139383
R_A^*	0.098392	0.209616	0.384579

Figure 8.

DISCUSSION

Though these project models are motivated by COVID, part of the project is hypothetical. We have a selection of parameters fixed corresponding to official data and by arbitrary choice, as well as working with those taking a range of values (both arbitrary or corresponding to the uncertainty we have with COVID).

Further developments of the models described are endless, yet a focus would be made on furthering the parameters and age groups for the structured models, as well as looking into vaccine immunity.

For vaccination, we ignored any delay of effect of vaccination and multiple doses, but we could develop our models by splitting the effect of the vaccination into many components. This is done by introducing the compartments for different level of protection from each strain with reduced risk of infection, reduced risk of hospitalisation/death and reduced risk of spread.

REFERENCES

Dowd J, Andriano L, Brazel D et al. Demographic science aids in understanding the spread and fatality rates of COVID-19. *Proceedings of the National Academy of Sciences*. 2020. doi:10.1073/pnas.2004911117

Restif O, Grenfell B. Integrating life history and cross-immunity into the evolutionary dynamics of pathogens. *Proceedings of the Royal Society B: Biological Sciences*. 2005. doi:10.1098/rspb.2005.3335

Restif O, Grenfell B. Vaccination and the dynamics of immune evasion. *Journal of The Royal Society Interface*. 2006. doi:10.1098/rsif.2006.0167

Gog J, Hill E, Danon L, Thompson R. Vaccine escape in a heterogeneous population: insights for SARS-CoV-2 from a simple model. *R Soc Open Sci*. doi:10.1098/rsos.210530

Diekmann O, Heesterbeek J, Roberts M. The construction of next-generation matrices for compartmental epidemic models. *Journal of The Royal Society Interface*. doi:10.1098/rsif.2009.0386

Burioni R, Topol E. Assessing the human immune response to SARS-CoV-2 variants. *Nat Med*. 2021. doi:10.1038/s41591-021-01290-0

APPENDIX A

Epidemic peak

$$\frac{dS}{dt} = 0 \implies \beta SI = 0 \implies S = 0,\ I = 0$$

$$\frac{dI}{dT} = 0 \implies \beta SI - \gamma I = 0 \implies S = \frac{\gamma}{\beta},\ I = 0$$

$$\frac{dR}{dt} = 0 \implies \gamma I = 0 \implies I = 0$$

$$\frac{\dot{S}}{S} = -\beta I \implies \int_0^t I\,dt = \frac{1}{\beta} ln\left(\frac{S_0}{S}\right)$$

$$\dot{S} + \dot{I} = -\gamma I \implies S + I = -\gamma \int_0^t I\,dt + S_0 + I_0$$

$$\therefore I = S_0 + I_0 - S + \frac{\gamma}{\beta} In\left(\frac{S}{S_0}\right)$$

Endemic equilibrium

$$\frac{dS}{dt} = 0 \implies I = \frac{\delta}{\beta}\left(\frac{N}{S} - 1\right)$$

$$\frac{dI}{dT} = 0 \implies I = 0\,, S = \frac{\delta + \gamma}{\beta}$$

$$\frac{dR}{dt} = 0 \implies \gamma I - \delta R = 0 \implies R = \frac{\gamma}{\delta} I$$

Next generation matrix method for hospitalisations

$$T = \begin{pmatrix} \beta & \tau\beta \\ 0 & 0 \end{pmatrix}$$

$$\Sigma = \begin{pmatrix} -(\gamma + \xi) & 0 \\ \xi & -\eta \end{pmatrix}$$

$$K = -T\,\Sigma^{-1}$$

Next generation matrix method for two age groups

$$T = \beta \begin{pmatrix} N_J & N_J \\ N_A & N_A \end{pmatrix}$$

$$\Sigma = \begin{pmatrix} -(\alpha + \delta_J + \gamma_J) & 0 \\ \alpha & -(\delta_A + \gamma_A) \end{pmatrix}$$

$$K = -T\Sigma^{-1}$$

Next generation matrix method for vaccination model 2

$$T = \frac{b}{\delta} \begin{pmatrix} (1-p)\beta_{NN} & (1-p)\beta_{VN} \\ p\beta_{NV} & p\beta_{VV} \end{pmatrix}$$

$$\Sigma = \begin{pmatrix} -v & 0 \\ 0 & -n \end{pmatrix}$$

$$K = -T\Sigma^{-1}$$

$$\mathscr{R}_0 = \left((1-p)\frac{\beta_{NN}}{n} + p\frac{\beta_{VV}}{v} + \sqrt{\left((1-p)\frac{\beta_{NN}}{n} - p\frac{\beta_{VV}}{v} \right)^2 + 4(1-p)p\frac{\beta_{NV}\beta_{VN}}{nv}} \right) \cdot \frac{b}{2\delta}$$

$$n = \delta + \alpha_N + \gamma_N$$

$$v = \delta + \alpha_V + \gamma_V$$

Disease-free equilibrium

$$\hat{S}_N = \frac{(1-p)\,b}{\delta}$$

$$\hat{S}_V = \frac{pb}{\delta}$$

$$\hat{I}_N = \hat{I}_V = \hat{R} = 0$$

Initial growth rate for 2 strain model

$$S = \frac{1}{\mathscr{R}_0}$$

$$R_1 = \frac{\gamma_1}{\gamma_1 + \mu + \sigma}(1 - \mathscr{R}_0)$$

$$\Lambda_2 = \beta_2(I_2 + I_{12})$$

$$\frac{dI_2}{dt} = \frac{\Lambda_2}{\mathscr{R}_0} - (\mu + \gamma_2)I_2$$

$$\frac{dI_{12}}{dt} = \frac{\gamma_1}{\gamma_1 + \mu + \sigma}\Lambda_2(1-\phi)(1-\mathscr{R}_0) - (\mu + \gamma_2)I_{12}$$

Summing these equations lead to the following differential equation,

$$\frac{d}{dt}(I_2 + I_{12}) = \left[\frac{\beta_2}{\mathscr{R}_0} + \frac{\gamma_1\beta_2}{\gamma_1 + \mu + \sigma}(1-\phi)(1-\frac{1}{\mathscr{R}_0}) - (\mu + \gamma_2)\right](I_2 + I_{12})$$

$$\frac{1}{I_2 + I_{12}}\frac{d}{dt}(I_2 + I_{12}) = \frac{\beta_2}{\mathscr{R}_0} + \frac{\gamma_1\beta_2}{\gamma_1 + \mu + \sigma}(1-\phi)(1-\frac{1}{\mathscr{R}_0}) - (\mu + \gamma_2)$$

By noting the basic reproductive rate of strain 1 and strain 2 to be,

$${}^1\mathscr{R}_0 = \frac{\beta_1}{\gamma_1 + \mu}$$

$${}^2\mathscr{R}_0 = \frac{\beta_2}{\gamma_2 + \mu}$$

$$\frac{1}{I_2 + I_{12}}\frac{d}{dt}(I_2 + I_{12}) = \beta_2\left[\frac{1}{{}^1\mathscr{R}_0} - \frac{1}{{}^2\mathscr{R}_0} + \frac{\gamma_1}{\gamma_1 + \mu + \sigma}(1-\phi)(1-\frac{1}{{}^1\mathscr{R}_0})\right]$$

We can solve to give an exponential model with growth rate,

$$r = \beta_2\left[\frac{1}{{}^1\mathscr{R}_0} - \frac{1}{{}^2\mathscr{R}_0} + \frac{\gamma_1}{\gamma_1 + \mu + \sigma}(1-\phi)(1-\frac{1}{{}^1\mathscr{R}_0})\right]$$

2 strain age-structured equations

$$\frac{dSJ}{dt} = \mu A - (\Lambda_1 + \Lambda_2 + \delta_J + \alpha)SJ + \sigma(RJ_1 + RJ_2 + RJ_{12})$$

$$\frac{dSA}{dt} = \alpha SJ - (\Lambda_1 + \Lambda_2 + \delta_A)SA + \sigma(RA_1 + RA_2 + RA_{12})$$

$$\frac{dIJ_1}{dt} = \Lambda_1 SJ - (\delta_J + \gamma_{J1} + \alpha)IJ_1$$

$$\frac{dIA_1}{dt} = \alpha IJ_1 + \Lambda_1 SA - (\delta_A + \gamma_{A1})IA_1$$

$$\frac{dIJ_2}{dt} = \Lambda_2 SJ - (\delta_J + \gamma_{J2} + \alpha)IJ_2$$

$$\frac{dIA_2}{dt} = \alpha IA_2 + \Lambda_2 SA - (\delta_A + \gamma_{A2})IA_2$$

$$\frac{dIJ_{12}}{dt} = (1-\phi)\Lambda_2 RJ_1 - (\delta_J + \gamma_{J2} + \alpha)IJ_{12}$$

$$\frac{dIA_{12}}{dt} = \alpha IJ_{12} + (1-\phi)\Lambda_2 RA_1 - (\delta_A + \gamma_{A2})IA_{12}$$

$$\frac{dIJ_{21}}{dt} = (1-\phi)\Lambda_1 RJ_2 - (\delta_J + \gamma_{J1} + \alpha)IJ_{21}$$

$$\frac{dIA_{21}}{dt} = \alpha IJ_{21} + (1-\phi)\Lambda_1 RA_2 - (\delta_A + \gamma_{A1})IA_{21}$$

$$\frac{dRJ_1}{dt} = \gamma_{J1} IJ_1 - [(1-\phi)\Lambda_2 + \sigma + \delta_J + \alpha]RJ_1$$

$$\frac{dRA_1}{dt} = \alpha RJ_1 + \gamma_{A1} IA_1 - [(1-\phi)\Lambda_2 + \sigma + \delta_A]RA_1$$

$$\frac{dRJ_2}{dt} = \gamma_{J2} IJ_2 - [(1-\phi)\Lambda_1 + \sigma + \delta_J + \alpha]RJ_2$$

$$\frac{dRA_2}{dt} = \alpha RJ_2 + \gamma_{A2} IA_2 - [(1-\phi)\Lambda_1 + \sigma + \delta_A]RA_2$$

$$\frac{dRJ_{12}}{dt} = \gamma_{J1} IJ_{21} + \gamma_{J2} IJ_{12} - (\sigma + \delta_J + \alpha)RJ_{12}$$

$$\frac{dRA_{12}}{dt} = \alpha RJ_{12} + \gamma_{A1} IA_{21} + \gamma_{A2} IA_{12} - (\sigma + \delta_A)RA_{12}$$

Here the Λ_i represents the force of infection of strain i as before, with $J + A = 1$,

$\Lambda_1 = \beta_{J1}(IJ_1 + IJ_{21}) + \beta_{A1}(IA_1 + IA_{21})$ and $\Lambda_2 = \beta_{J2}(IJ_2 + IJ_{12}) + \beta_{A2}(IA_2 + IA_{12})$.