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Modelling of infectious diseases

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Abstract

With the increasing awareness of the potential for diseases to mutate into novel strains, it is important to be able to model the propagation of multi-strain diseases. This report aims to look at various epidemic models in order to understand the dynamics of disease propagation. We will study various models that incorporate vaccination. In particular, we will study models that account for genetic heterogeneities in pathogens and propose a model that describes two-strain diseases with vaccination.

1 Introduction

This report will discuss various models describing disease propagation. Studying the dynamics of disease propagation leads to the understanding of epidemiological events, such as whether a disease will become endemic in a population or whether an epidemic will occur.

Most models will include at least two non-intersecting compartments: the susceptible population and the infected population. The models build off these basic compartments, incorporating new compartments such as a compartment for those with immunity due to recovery from the disease, those under a control strategy such as vaccination, treatment or quarantine and compartments for different pathogen variants.

We will begin with a basic model called the SIR model and look at extensions of this that incorporate vaccination. We will then incorporate pathogen heterogeneity by considering models with two strains. Finally, we will propose a model that describes the dynamics of two-strain diseases with vaccination under certain assumptions.

2 Preliminary models

Definition 2.1 The *basic reproduction number*, R_0, is the number of secondary infections one infectious individual will produce if the whole population is susceptible.

Note that theoretical expressions for R_0 is different for different models and methods of derivation. However, it is mandatory that these expressions can be interpreted to fit the definition stated. Also note that a more infectious disease generally has a higher R_0.

2.1 SIR model

We introduce the SIR model. The SIR model is a basic model introduced by Kermack and McKendrick in 1927 [1].

In the model, there are three non-intersecting classes of individuals. Let S denote the susceptible class, let I denote the infected class and let R denote the recovered class. Let $N = S + I + R$ be the total population.

The model makes the following assumptions:

- The total population is constant.
- Recovered individuals are immune to the disease.
- Infected individuals are also infectious. That is, if an individual has the disease, they are able to pass it onto others.
- No births and deaths.

Remark 2.2 The assumptions stated are restrictive. By assuming N constant means that the model is only useful for short time periods. However, childhood diseases such as smallpox and rubella are modelled well by the fact that the recovered class has permanent immunity.

The governing differential equations are as follows:

$$\begin{aligned} I'(t) &= \beta SI - \alpha I \\ R'(t) &= \alpha I \\ S'(t) &= -\beta SI \end{aligned} \tag{2.1}$$

where the parameters are

Parameters	
β	transmission rate constant
α	recovery rate
$\lambda = \beta I$	force of infection

The report will essentially study models that are more complicated versions of the SIR model. Some models that this report does not cover include the SEIR model, where we remove the assumption that

infected individuals are infectious by adding an extra compartment E denoting the exposed/latent class. Essentially, this class represents those who are infected, but are not yet infectious. This is because the pathogen needs time to establish itself in the host.

2.2 SIR model with vaccination

We will now include vaccination in the SIR model stated in 2.1. Essentially, vaccines provides protection against particular diseases by inserting weakened or dead pathogens in an individual's body. This is so the individual's immune system can recognise the pathogen much faster in the future, providing protection from that disease.

Let p be the proportion of the population vaccinated and let ω be the waning rate of vaccine-induced immunity against a particular disease.

The governing differential equations are found in [5] and is as follows:

$$\begin{aligned} S'(t) &= (1-ep)\mu N - \beta SI + \omega V \\ V'(t) &= ep\mu N - \mu V - \omega V \\ I'(t) &= \beta SI - \alpha I - \mu I \\ R'(t) &= \alpha I - \mu R \end{aligned} \tag{2.2}$$

where the parameters are as defined before and

Parameters	
μ	death rate
e	proportion of vaccinated population protected by the vaccine

Note that the model accounts for births and deaths. However, they occur at the same rate, so N is still constant. The model assumes that some fraction p of the population is vaccinated at birth.

2.2.1 Perfect vaccine with life-long vaccine-induced immunity

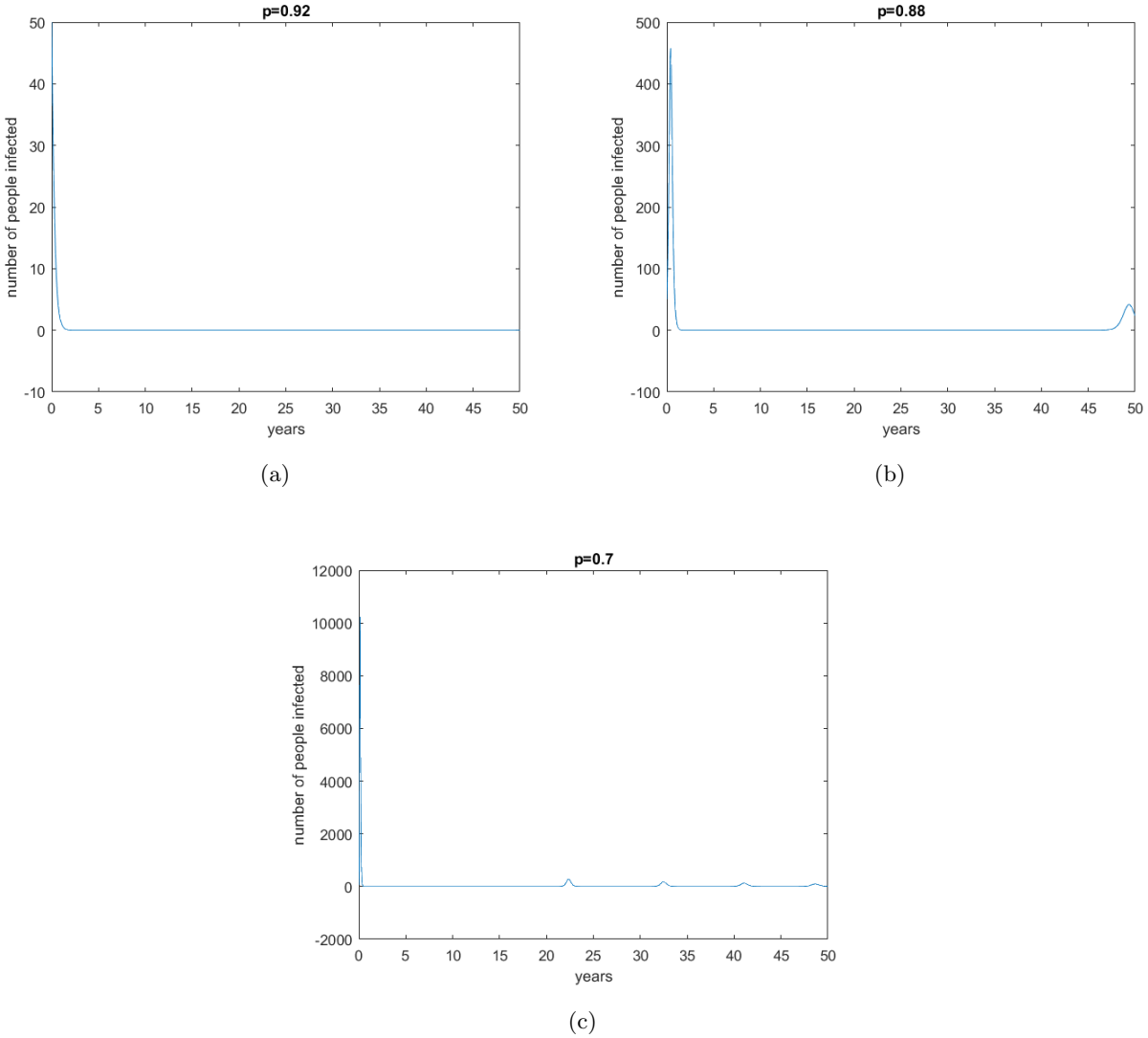
In order to eradicate a disease in a population, we must meet certain requirements. Assume for this subsection that the vaccine is perfect. That is, $e = 1$. This also means that the vaccine has a vaccine efficacy of 100%, which is discussed further in the following sections. Also, we assume that immunity due to the vaccine is lifelong.

Observation 2.3 $R_0 < 1$ in order for the system to approach the disease-free equilibrium.

Definition 2.4 R_c is the *controlled reproduction number* and it gives the number of secondary cases one infectious individual creates in a population of susceptibles with a control strategy in place.

Because we are considering vaccination, we require $R_c < 1$ in order to eradicate the disease. Let $q = 1 - p$. We have $R_c = qR_0 < 1$. Using this, we can define the *critical vaccination proportion*, $p_c = 1 - \frac{1}{R_0}$. In order to eradicate the disease, we need $p > p_c$. This is under the assumption that the vaccine is perfect and that vaccine-immunity is lifelong.

We use the parameter values in [5]. In particular, $R_0 = 11.15$. We apply a vaccination at $t = 0$ years.



(a) (b) (c)

Figure 1: Results for different values of p

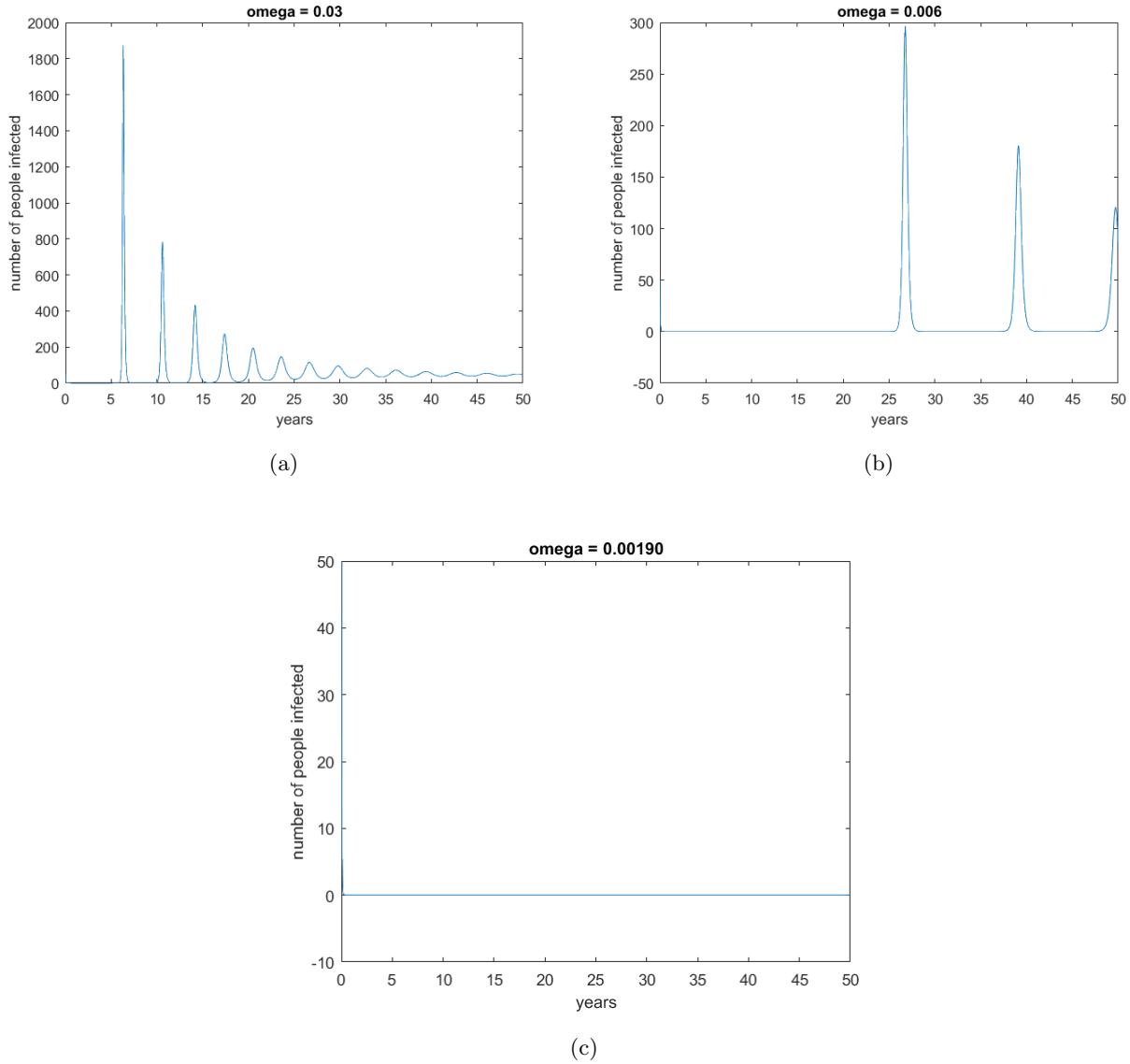
Notice that for the different values of p in figure 1, we have different results. In figure 1a, the disease

is eradicated. In both figure 1b and 1c, there is an apparent eradication of the disease. However, after some time, we see a small peak occurring, showing an *epidemic*. The period of apparent eradication is called the *honeymoon period*, where supposedly the disease is eradicated. However, it is still prevalent at a very low number. Note also that epidemics occur more often if $p << p_c$.

2.3 Perfect vaccine with waning vaccine-induced immunity

In order to eradicate the disease, we must be below some critical waning rate value ω_c to eradicate the disease. The critical waning rate is given by $\omega_c = \dfrac{\mu}{1 - R_0}[R_0(1 - ep) - 1]$ for 2.2.

As before, using the parameter values in the previous model 2.2, we obtain the following results:



(a) (b) (c)

Figure 2: Results for different values of ω

We notice similar results as in the life-long vaccine-induced immunity case. Notice then when $\omega > \omega_c$, epidemics occur. Also, when ω is large, epidemics occur more often. This is because individuals are losing immunity too quickly and hence the disease cannot be eradicated.

3 Two-strain models

We consider models which take into account genetic variants of pathogens. We will state and describe two two-strain models in the follow subsections.

If we modelled two strains using the SIR model, competitive behaviour between the two strains occurs. Pathogen variants are essentially competing for the same resources, that is, susceptible individuals. The result of this competitive behaviour is summarised in the following observation.

Observation 3.1 Let R_1, R_2 denote the basic reproduction numbers of two different strains of a pathogen.

1) If $R_1 < 1$ and $R_2 < 1$, then both strains are eliminated. The system will approach the disease-free equilibrium.

2) If one of R_1 and R_2 is greater than one, than the strain with $R_j > 1$ will persist.

3) If both R_1 and R_2 are greater than one, then the strain with the greater R_j will persist.

However, in reality, there are more factors to consider than modelled by the SIR model. We know that multiple strains can coexist.

Coinfection, which is the process in which a host is infected with multiple strains of a pathogen or two or more distinct pathogens, is common in strains that cause HIV [3]. This is one mechanism for *coexistence*, where multiple strains of a pathogen are prevalent in the population.

Another mechanism for coexistence is due to the *mutation* of pathogens, which are changes in DNA of an organism that could lead to resistance against an individual's immune system. We can account for this by including a term that transfers strain one to strain two showing the evolution of the strain one. In this case, it is intuitive that there are cases where we have $R_2 < R_1$, strain two persists in the population.

When a pathogen has multiple variants, vaccinating an individual against the pathogen may not result in protection against all variants. This is because a vaccine only contains multiple weakened or inactive strains of a particular pathogen. This means that the individual's immune system is able to recognise these particular pathogen variants much faster in the future. This may not be the case for strains not included in the vaccine. Hence, while vaccination provides protection for the variants

included in the vaccination itself, it provides limited to no protection against strains not included in the vaccine.

It is worth noting that biologists have found that there has been an increase of genetic diversity in pathogens upon the introduction of vaccines, as variants included in the vaccines are driven to elimination, so those strains that are resistant to the effects of vaccination can become prevalent in the population.

3.1 Implications of an imperfect vaccination

It is worth mentioning the complications of imperfect vaccination in a model. In [2], a simple SIS model with continuous vaccination was analysed. Results show that implementing an imperfect vaccination model can lead to a backward bifurcation. Hence, an *endemic equilibrium*, an equilibrium in which the disease persists, may exist even if $R_0 < 1$. We may need to reduce R_0 well below one to where there are no endemic equilibria. Although it seems harder to eliminate a disease with an imperfect vaccine, the region in which the disease-free equilibrium is *locally stable*, which is the equilibrium the system tends towards if initial conditions are close enough, is much larger.

For a imperfect vaccine, if the vaccination intake rate was 0, then no backward bifurcation occurred. This was also the case for a perfect vaccine. For these cases, when $R_0 < 1$, the disease-free equilibrium is *globally stable*, that is, all solutions tend towards that equilibrium for all initial values.

3.2 Two-strain model with mutation, vaccination and immunity upon recovery

The following model is from [5].

$$\begin{aligned}
V'(t) &= p\mu N - \beta_w(1-\phi_w)VI_w - \beta_r(1-\phi_r)VI_r - \mu V \\
S'(t) &= (1-p)\mu N - (1-Q)\beta_w SI_w - Q\beta_w SI_w - \beta_r SI_r - \mu S \\
I_w'(t) &= (1-Q)\beta_w SI_w + \beta_w(1-\phi_w)VI_w - \alpha I_w - \mu I_w \\
I_r'(t) &= Q\beta_w SI_w + \beta_r SI_r + \beta_r(1-\phi_r)VI_r - \alpha I_r - \mu I_r \\
R'(t) &= \alpha I_w + \alpha I_r - \mu R
\end{aligned} \tag{3.1}$$

I_w denotes the wild-type strain and I_r denotes the mutant, vaccine-resistant strain.

Note some of the key differences between model 2.2 and 3.1. e and ϕ do not convey the same meaning. e is the vaccine intake, while ϕ is the *vaccine efficacy*, which is the proportion decrease of risk of those who are vaccinated compared to those who are not vaccinated. It is given by

$$\frac{\text{risk among unvaccinated group - risk among vaccinated group}}{\text{risk amoung unvaccinated group}}$$

Notice in 3.1, in the first equation we have the term $p\mu N$, while in 2.2 we have $ep\mu N$, where we have set $e = 1$. Hence, both of them has set the vaccine uptake equal to one, except in 3.1, e is not explicitly shown in the equation. Both e and ϕ need to be equal to one for a perfect vaccine.

One of the new parameters is Q, which accounts for mutation. Notice in the equation for I'_w, we have the term $(1 - Q)\beta_w SI_w$. Some fraction Q of that term is transferred to the I'_r equation, accounting for the mutation of the wild-type strain into the mutant strain. Hence, the model assumes that there is some continuous mutation of I_w into I_r.

The other assumptions are stated below:

- In the absence of vaccination, the mutant is at a selective disadvantage as the wild-type strain is more infectious (higher β) than the mutant strain.
- The vaccination gives stronger protection against the wild-type strain. That is, $\phi_w > \phi_r$.
- Recovering from one strain confers life-long immunity to all other strains.
- N is constant.
- Total birth and death rates are equal.

We use the parameter values in [5]. In particular, we set $p = 0.85$, $\beta_w = 0.0029$, $\beta_r = 0.00145$, $\phi_w = 0.95$, $\phi_r = 0.5$, $Q = 0.0001$, $\mu = 0.02$, $\alpha = 26$ and $N = 10^5$.

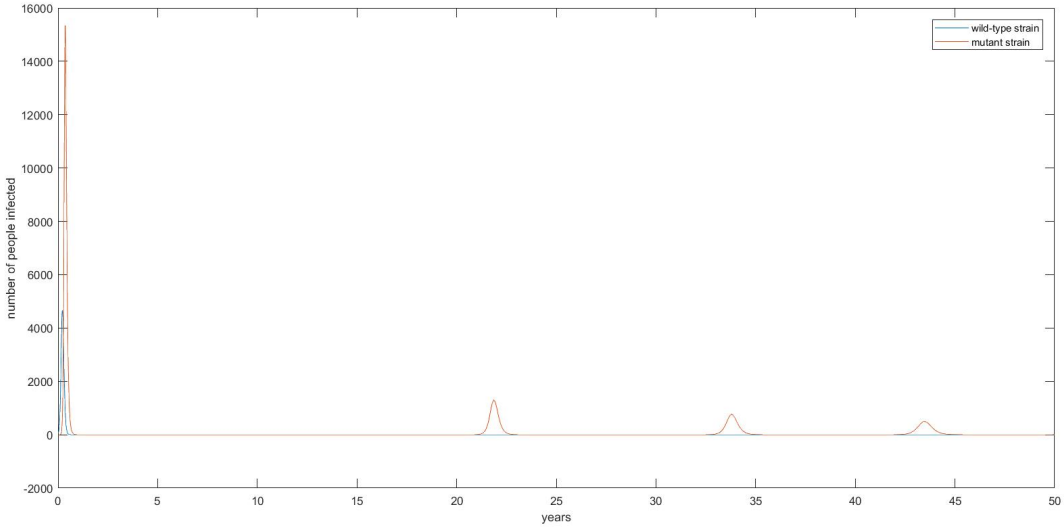


Figure 3: Two-strain model results

Notice that the wild-type strain is eliminated by the vaccine. Moreover, we see that as the wild-type strain decreases in prevalence, the mutant strain increases in prevalence. We also see epidemics occurring caused by the mutant strain. This is because the vaccine is only somewhat effective against the mutant strain.

3.3 Two-strain model with vaccination and recovery into the susceptible population

One assumption made in 3.1 was that upon recovery from either strain, one obtains full and life-long immunity to both strains. Recall that vaccination essentially inserts a weakened of dead pathogen into the individual. Hence, if vaccination does not give full and life-long immunity, one should not expect that recovery from the disease itself gives full and life-long immunity. The human immune system does not distinguish between vaccines and natural infections [4]. Active responses are formed from both cases and so it is reasonable to place immunity due to vaccination and immunity upon recovery in the same compartment.

The following model is from [2]. It accounts for two different strains of a particular disease, but does not have any term accounting for mutation. Rather, it models the fact that a particular vaccine will only protect against one of the strains and confers some protection against the other. Moreover, once an individual recovers from strain one, they are susceptible to either strains. In the model, I_v is the strain included in the vaccine while I_w is not.

$$\begin{aligned}
S'(t) &= \Lambda - \frac{\beta_w S I_w}{N} - \frac{\beta_v S I_v}{N} - (\mu + \psi)S + \chi\gamma I_w + \alpha I_v \\
I_w'(t) &= \frac{\beta_w S I_w}{N} + \frac{\beta_w(1-\phi_w)V I_w}{N} - (\mu + \gamma)I_w \\
I_v'(t) &= \frac{\beta_v S I_v}{N} - (\mu + \alpha)I_v \\
V'(t) &= \psi S - \frac{\beta_w(1-\phi_w)V I_w}{N} + (1-\chi)\gamma I_w - \mu V
\end{aligned} \tag{3.2}$$

The parameter Λ denotes birth rate. It is assumed that the total birth and death rates are equal. That is, N is constant. However, instead of having some proportion of births go into the susceptible and vaccinated class as in 3.1, in this model, all births are placed into the susceptible class and the susceptible class is vaccinated at some rate ψ. For vaccines that are taken not long after birth, the assumption in model 3.1 could work.

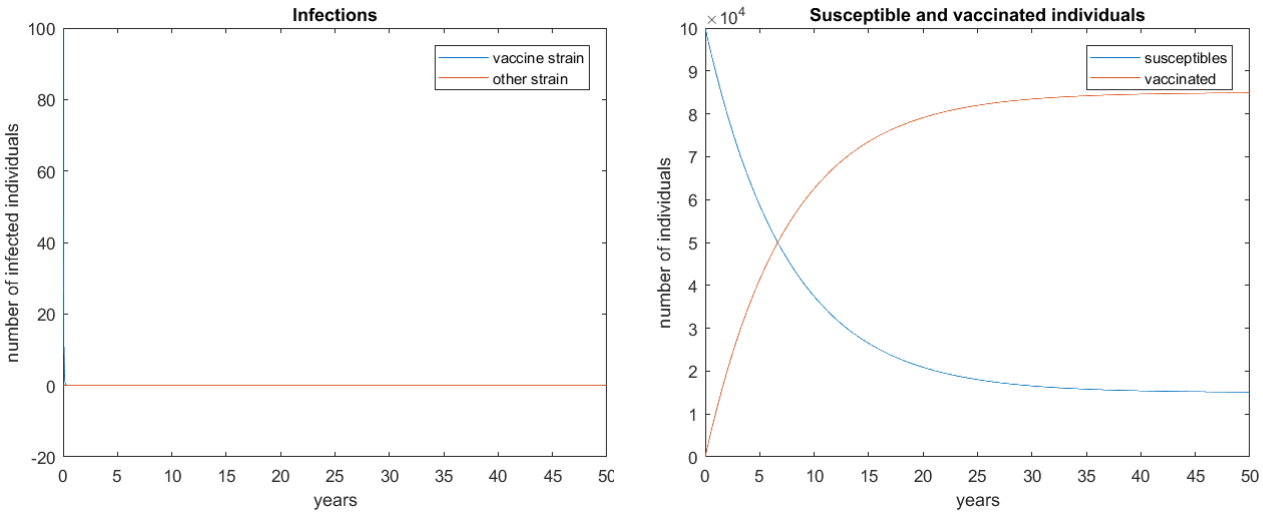
Moreover, 3.2 uses standard incidence $\frac{\beta SI}{N}$. This incidence term describes diseases that are not affected greatly by population changes such as sexually transmitted diseases. This is because contact

rate cannot increase indefinitely. Model 3.1on incidence βSI, which is more sensitive to population changes as this changes contact rate. Diseases such as influenza fit this criteria. For a constant population, mass action incidence and standard incidence agree on results.

Note that both γ and α are recovery rates of the respective strains. χ is the proportion that recover to susceptible class. We see that model 3.2 treats recovered individuals as vaccinated individuals. These vaccinated individuals are not fully protected and they can get infected at a reduced rate by strain I_w. Strain I_v can only infect susceptible individuals due to the vaccine.

Parameter values were chosen such that they were equivalent to the values in model 3.1 for comparison. We also make $\alpha = \gamma$ by assuming that the strains are similar enough that the recovery rates are the same.

Note the vaccine is considered perfect for the vaccine strain.



(a) (b)

Figure 4: Results for this model

The parameter values are stated:

Parameters		Parameters	
Λ	2000	ψ	0.1133
β_w	0.00145	χ	0.5
β_v	0.0029	$\gamma = \alpha$	26
μ	0.02	ϕ_w	0.5

Notice $\Lambda = \mu N = 2000$ in order to match the parameter values in model 3.1. Moreover, in model

3.1, 85% of the population was vaccinated. To match this, we find an expression for the disease-free equilibrium $\epsilon^* = (S^*, 0, 0, V^*)$. Using the fact that $N \to \frac{\lambda}{\mu}$, we find that the proportion vaccinated at the disease-free equilibrium is $\frac{\psi}{\psi + \mu}$. By setting this equal to 0.85, we get $\psi = 0.1133$.

Notice that in figure 4, that both strains are eliminated even though we have tried to match the parameters of the two models. This shows that model 3.2 describes different dynamics. In particular, it does not account for mutation, so there is no direct transfer between the vaccine strain to the other strain. Also note the incidence terms, with N in the denominator. N is large and hence those incidence terms are small, so the number of infected individuals have a low rate of change.

In [2], the theoretical expressions for the the basic reproduction numbers are $R_w = \frac{\beta_w(\mu + (1-\phi_w)\psi)}{(\mu+\gamma)(\mu+\psi)}$ and $R_v = \frac{\beta_v \mu}{(\mu+\alpha)(\mu+\psi)}$.

Substituting the values in, we find that $R_w = 32.04 \times 10^{-6}$ (4sf) and $R_v = 16.72 \times 10^{-6}$ (3sf). Hence, because their controlled reproduction numbers are less than one, both strains die out in the model.

4 Proposed model

The model proposed [1] is an attempt to describe two-strain dynamics of a disease that fits the described assumptions. One example that may fit the assumptions below is the influenza virus, although the model does not include the latent period. We combine different properties of the models studied in the previous sections and consider the case with two strains introduced into the population.

Suppose that a well-studied strain I is included in the vaccine, while a lesser-known strain J is not. We assume that the first vaccine will fully protect against strain I and will provide some protection against J. Also, we assume that recovering from strain I gives immunity for strain I and provides some protection against strain J. This means that once an individual has recovered from a particular strain, it has the same effect as being vaccinated with that strain.

We also use mass action incidence, as diseases such as influenza is density dependent. However, we will not account for variations in population.

We will assume that after some time t_0, a vaccine containing both strains will be available.

[1] From the best of my knowledge, this model has not been proposed before.

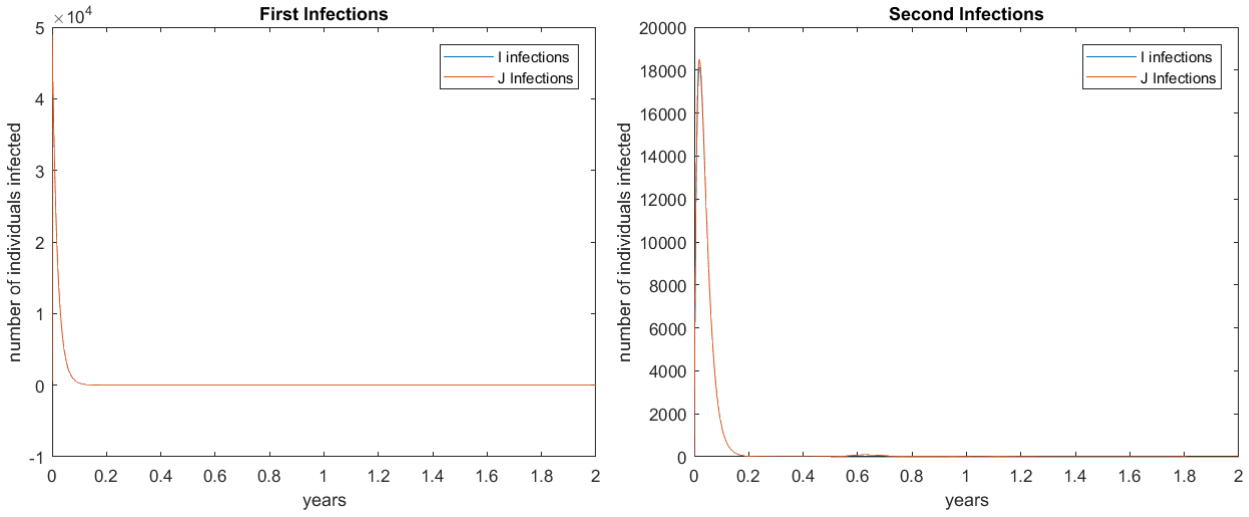
$$
\begin{aligned}
S'(t) &= \Lambda - \beta_1 S(I + I_0) - \beta_2 S(J + J_0) - (\mu + \psi)S \\
I'(t) &= \beta_1 S(I + I_0) - (\mu + \gamma)I \\
J'(t) &= \beta_2 S(J + J_0) - (\mu + \alpha)J \\
V_I'(t) &= \psi S H(t_0 - t) + \gamma I - \sigma\beta_2 V_I(J + J_0) - \mu V_I \\
V_J'(t) &= \alpha J - \sigma\beta_1 V_J(I + I_0) - \mu V_J \\
I_0'(t) &= \sigma\beta_1 V_J(I + I_0) - (\mu + \gamma)I_0 \\
J_0'(t) &= \sigma\beta_2 V_I(J + J_0) - (\mu + \alpha)J_0 \\
V'(t) &= \psi S H(t - t_0) + \gamma I_0 + \alpha J_0 - \mu V
\end{aligned} \tag{4.1}
$$

where H is the heaviside step function.

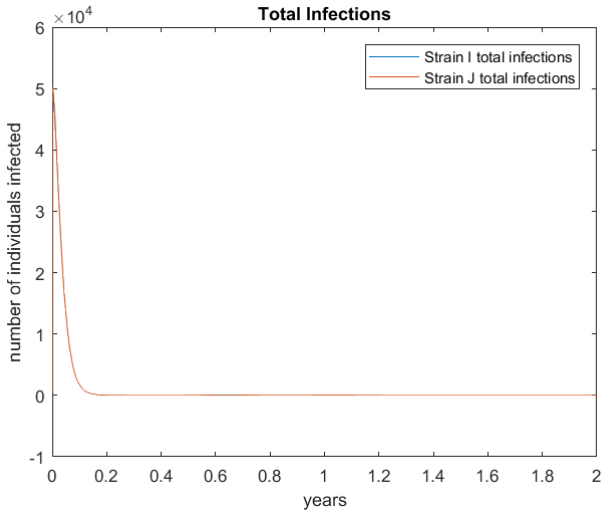
The model has several extra compartments compared to the previous models discussed. The V_I and V_J compartments are for those that have recovered or have received vaccinations for only one of strain I or J respectively. V is the compartment for those who have recovered or received vaccinations from both strains I and J. I_0 is the compartment for those who are infected with strain I, but have previously recovered from strain J and similarly for J_0.

The parameter σ is defined as $1-\phi$, where ϕ is the vaccine efficacy. Notice that this term accounts for the fact that, for example, if an individual recovers from strain I, they can be infected by strain J at a reduced rate. We have assumed ϕ is the same for both cases.

We graph the model with the following parameter values that are realistic for influenza:



(a) (b)



(c)

Figure 5: Results for the proposed model

Parameters		Parameters	
Λ	2000	ϕ_w	0.5
β_1	0.4	ψ	104
β_2	0.4	χ	0.25
μ	0.02	$\gamma = \alpha$	52

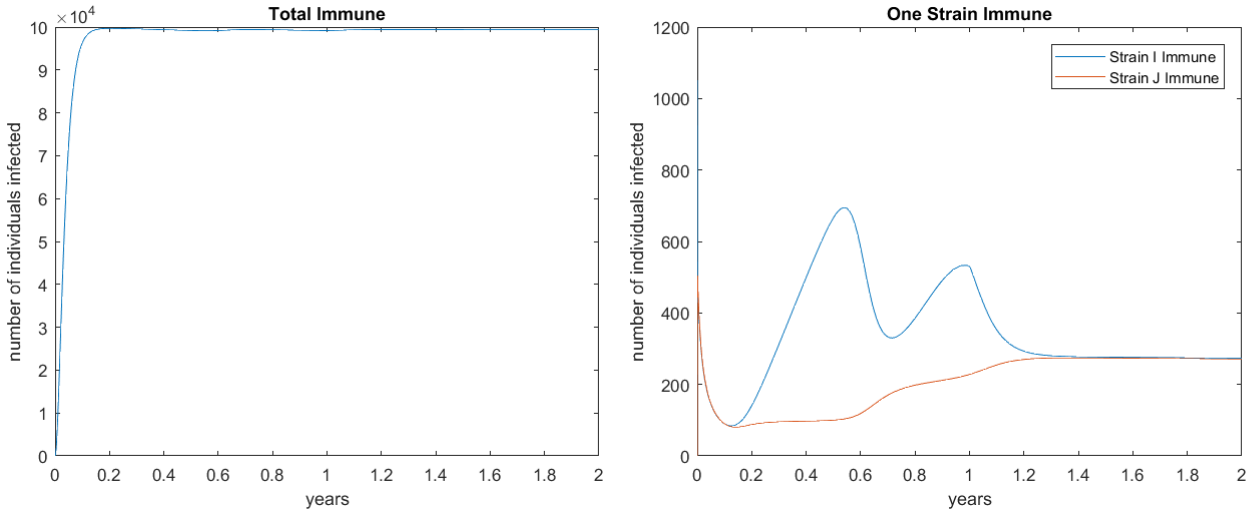
We have assumed that both strain I and J have the same β values. β_1 and β_2 were set to 0.4 as it lies within the range stated in [6].

It is generally thought that being infected with influenza lasts three to seven days, though it may

reach up to two weeks. We have assumed that an individual will recover after one week. That is, $\alpha = \gamma = 52$. Also, we have set $I(0) = J(0) = 500$. As before, the proportion vaccinated with the second vaccine in the long run is given by $\frac{\psi}{\mu + \psi}$. With $\psi = 104$, 99.98% of individuals will be vaccinated in the long run.

It appears that for the influenza virus, the recovery rate is fast enough that many individuals develop immunity to the present strains and hence the prevalence of the strains become very low after a short time. The second vaccine with both strains is applied at $t = 1$ years, but by then, most individuals have acquired immunity against both diseases. In reality, the World Health Organisation predicts what strains will become prevalent in the future. In the model, we have incorporated a new vaccine after 1 year as a response to strain J becoming prevalent in the past.

It is interesting to note the that at around $t = 0.6$ years, strain J has a small epidemic, before the application of the second vaccine. It is hard to see this in figure 5c, but it can be seen more clearly in the figure 5b, which plots I_0 and J_0. Note that the number of total infections is just $I + I_0$, which is what is plotted in figure 5c. Hence, we may expect these small epidemics to occur if the second vaccine was not applied to the model.



(a) (b)

Figure 6: Results for proposed model

The disease-free equilibrium is $\epsilon^* = (S^*, 0, 0, 0, 0, 0, 0, V^*)$, where $S^* = \frac{\Lambda}{\mu + \psi}$ and $V^* = \frac{\psi\Lambda}{(\mu + \psi)\mu}$. We should have $V_I = V_J = 0$ if the system is indeed approaching the disease-free equilibrium. However, in figure 6b, which corresponds to V_I and V_J, approaches a non-zero equilibrium. This may be because the β value of influenza is quite high, which means that the two strains can infect the population at

a faster rate, resulting in the two strains becoming endemic. This means that there are always a few individuals recovering into class V_I and V_J while a few individuals are being infected a second time by the other strain. It is interesting to note that when we set ψ to be very large, V_I and V_J do indeed approach 0. Hence, we need to vaccinate almost all individuals in order to eradicate both strains and reach the disease-free equilibrium. Moreover, with the current ψ value, we could expect to see small epidemics occurring as the prevalence of the two strains is non-zero.

5 Conclusion

The aim of this project has been to study various different models of infectious diseases and to propose a model.

It seems that the proposed model is quite limited. While we could interpret the results in a biological sense, it does not reflect what happens in reality, at least in the case of influenza. For example, the model includes only two strains, so while many individuals develop immunity to the two strains after a short time, the high mutation rates of influenza mean that new strains may have arisen and individuals could still get sick despite of immunity to the two strains. Therefore, despite the low prevalence of the two strains, there may be other strains that are causing epidemics. Moreover, we have added a second vaccine as a response to strain J becoming prevalent. In reality, strains that may become prevalent are predicted in order to prevent epidemics.

It is also hard to consider exactly how much protection recovery from one strain confers to the other strain. Further research into the complex make-up of the strains and how the immune system differentiates between strains could be incorporated to more accurately represent ϕ. More interestingly, analysis that goes further than plotting results on the model could be done. Moreover, including mutation in the proposed model, applying a vaccination for upcoming future strains and finding an optimal time between vaccinations are areas that could be pursued in the future.

6 Acknowledgments

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