Modelling Infectious Disease Epidemiology and Vaccination Impact

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Abstract

This thesis presents mathematical models for the dynamics of vaccine preventable diseases, specifically looking at the New Zealand situation. Through the use of integral and differential equations, we develop models and compare the results of these to known data.

Using game theory analysis we determine and compare the proportion of the population that needs to be vaccinated in order to minimise the expected costs to the individuals in the population and to the community. Two different scenarios and methods are considered, where the effects of vaccination last only one epidemic cycle (using an integral equation method) and where vaccination is effective over an entire lifetime (using a differential equation method). For both scenarios, we find that the minimum cost for the individuals is reached when a lower proportion of the population is vaccinated than needed for the minimum cost to the community.

We then elaborate on the integral equation method to produce a model for repeated epidemics of measles in a population, where a discrete mapping is used to include the year to year demographics of the population. The results of this model show a different epidemic pattern then that produced from a differential equation model, with numerical problems encountered. From here on, we use differential equation models in our analysis.

A critique and extension to an existing model for the dynamics of the hepatitis B virus is presented, with discussion on the appropriateness of the model's construct for predicting the incidence of infection. Alternative differential equation models for hepatitis B virus and immunisation that include splitting the population into age groups with non-homogeneous mixing are presented. The results of these models are compared with the known data on incidence of infection and carriage in New Zealand, showing how affective different immunisation schedules may have been.

Differential equation models are then presented for meningococcal B virus epidemiology in New Zealand, with the models incorporating different features of the virus until the best model is found that fits the New Zealand data. Each model is compared with the known incidence of infection, with the population being either treated as a whole or split into age groups with non-homogeneous mixing. The effect of vaccination is included in this model so that we can explore the future of the infection in the population, and how best to tackle any future epidemics. The model shows that the current vaccination campaign was the best solution for controlling the epidemic, but there will be epidemics in the future that will need subsequent vaccination campaigns to limit the number of infections.

Acknowledgements

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Lastly, my thanks to my family for seeing me through to the end of my studies, to Mum and Kenny for their love and support each day.

Dedicated to Ian Mann, 1942–2005.

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Chapter 1

Introduction

When the incidence of an infection starts to increase in any population, people start to look at how best to combat the outbreak or at least to curb the number of infections. Launching nationwide vaccination campaigns (or even vaccinating a small group of a population) can be a costly and time consuming endeavour, so any tool that will enable the campaign to be more directed or to predict the outcome is highly valuable.

Daniel Bernoulli developed a mathematical model of the impact of vaccination against smallpox in 1760, and since then there has been an increasing number of mathematical epidemiology papers published. Using mathematical models, we gain a better understanding of the dynamics of the infection and some of the underlying features of infections that may not be easily observed, for example the carriage state of hepatitis B virus, where people can be infectious but shows no outward signs of infection. These people could play a key role in aiding the control of an epidemic, yet in practice it is hard to identify the role they have in the epidemic process – hence there is a need for models that allow us to take these aspects into consideration to better implement control measures.

Anderson & May (1992) give a background to the use of mathematics to study infectious diseases, with reference that the more recent publications tend to focus on the use of models to influence public health policy for disease eradication or control. As a more recent example, mathematical models were utilised in the control of the outbreak of foot and mouth disease in the United Kingdom (Kao, 2002), with an emphasis that these models need to be accessible and understandable to those making the policy guideline. This was also echoed in Regan & Wilson (2008), discussing the use of mathematical models for sexually transmitted infections, and the need for models to reflect and explain the known data. Glasser *et al.* (2004) give a brief outline of selected cases internationally where mathematical models have influenced public health policy. In New Zealand, mathematical models have been used in the past by the Ministry of Health when making decisions about vaccination policy and healthcare (for example Roberts (2000a), Tobias *et al.* (2002) and, Tobias & Cheung (2002)).

In this thesis, we aim to construct new mathematical models for diseases in New Zealand, and investigate the impact of vaccination on the epidemic's progress.

1.1 Background Information

Although the meanings of vaccination and immunisation are not equivalent, we shall use vaccination to mean that a person has been treated with a preventative medicine - whether it is through a vaccine or an immunisation. The difference in the terms vaccination and immunisation can be seen in Macpherson (1992): Immunisation – "the introduction of antigens into a body to produce immunity." Whereas, "Vaccination, from *vacca*, Latin for cow, means inoculation with the material of cowpox, performed to afford protection to the inoculated person against an attack of smallpox, or at all events with the view of diminishing the seriousness of, and averting a fatal result from, any such attack. This is the strict sense of the term, but it is used nowadays to describe the process of inoculating with any vaccine to obtain immunity, or protection, against the corresponding disease."

Throughout this thesis we use the basic reproduction ratio, R_0, to measure the rate at which an infection spreads through a population. The basic reproduction ratio is defined as the expected number of secondary cases of infection that would occur due to a primary case in a fully susceptible population. See, for example Anderson & May (1992) and Diekmann & Heesterbeek (2000). If $R_0 < 1$, then there may be a few cases of infection, but, on average, an infectious person will infect less than one other person, so an epidemic cannot occur. If $R_0 > 1$, then an epidemic is going to occur, as an infected person is infecting more than one other person.

In a model with age structure, to calculate the basic reproduction ratio we need to calculate the next generation matrix – then R_0 will be the largest eigenvalue of this matrix (Diekmann & Heesterbeek, 2000). The next generation matrix is structured according to infection type – for our models this is usually infectious or carriers in each of our age groups. The entries in the next generation matrix can then be thought of as basic reproduction ratios for each type of infection: an entry in the i^{th} row and j^{th} column is the expected number of type "i" infections caused by a single type "j" infectious person in a fully susceptible population. Some estimates of R_0 values for various infections and different locations are given in the Table 1.1.

1.2 Outline of the thesis

We begin the thesis with a look at what proportion of the population needs to be vaccinated in order to minimise the cost to an individual and to the community as a whole. After introducing a vaccine into a population to combat a current or potential epidemic, a debate arises about whether to enforce vaccination or leave the decision to individuals. The choice of vaccination policy can cause different outcomes for the community as a

Measles		Other Infections	
Location	Estimate of R_0	Infection and location	Estimate of R_0
Italy	6.1	Mumps in 'Europe'	3.6 - 4.5
'Europe'	9.6	Rubella in 'Europe'	3.4 - 6.4
UK and USA	12 -13	Pertussis in USA	3.7 - 5.4
New Zealand	12.8	Pertussis in New Zealand	15.8
Ghana	14 -15	Pertussis in UK	16 -18
Nigeria	16 -17	Smallpox (developing countries)	3 - 5
Niger	18.8	Polio (developing countries)	5 - 7
		HIV in UK, homosexual males	2 - 5
		HIV in Uganda, heterosexuals	10 -11
		SARS in 2003	3.3

Table 1.1: Some estimates of R_0 for measles and other infections (information obtained through a private communication with M. Roberts).

whole; the best strategy for enforced vaccination may require a different proportion of the population vaccinated than what would occur if left to individuals to decide. In the second chapter we explore the proportion of the population that is required to be vaccinated in order to minimise the cost to individuals and to the community as a whole when two strategies are available to them: remain susceptible and risk infection, or be vaccinated and not risk infection. The methods used in this chapter (a simple SIR model and an integral equation model) serve as an introduction for the rest of the thesis, where both these methods are used and expanded.

The third chapter presents an integral equation model for repeated epidemics that occur within a year, with a discrete map that allows us to include the demographic changes in the population at the end of an epidemic. The population is split into four age classes, and the number of people infected each year is calculated. This is then compared to the known data on measles epidemics in New Zealand, and to a past model that successfully predicted a measles epidemic. The model results from the integral equation method are different to those from the differential equation method (which showed a strong match to the known data), and numerical problems arose when solving the integral equation. For these reasons, we changed our approach on modelling to use differential equation methods for the subsequent chapters.

The fourth and fifth chapters deal with modelling the epidemiology of Hepatitis B infection. Chapter Three gives a literature review of models of this disease, and then focuses on Medley *et al.* (2001). A previous model (Edmunds *et al.*, 1993) showed that the probability of developing the carriage state depends on the age at infection, and in Medley *et al.* (2001) they assume this probability is a function dependant on the force of infection, that is inversely related to the age at infection. By making this assumption, their model produces a backwards bifurcation, showing that infection can persist even when the basic

reproduction ratio is less than one. We then extend this model to a population split into two age groups, where the probability of developing carriage is made constant for each age group, to see if the results from the single population model can be replicated. However, the two-age-group model does not produce the backwards bifurcation seen in Medley *et al.* (2001), but gives a high yearly incidence of infection with a large number of carriers always present in the population.

In Chapter Five, we narrow our focus to modelling the hepatitis B situation in New Zealand by developing a different differential equation model to best fit the known data. Hepatitis B has the second highest death rate for a vaccine preventable disease in New Zealand (New Zealand Ministry of Health, 2002), so producing a model that can explore the effects of vaccination schedules would be of great benefit. Vaccination against hepatitis B was only introduced in 1985, with a catch up campaign in 1988 to immunise all preschoolers, and is still a routine infant vaccination. The recorded data for incidence of hepatitis B infection is hard to analyse, as data before 1984 included both acute infections and notifications of the chronic carrier state. One of the interesting features of hepatitis B is that acute cases can be asymptomatic, with the symptomatic infection becoming more likely with increasing age. We develop a model incorporating the different probabilities for developing carriage and presenting symptoms depending on age, and include the effects of vaccination. We then explore the outcome on the incidence of infection on alternative vaccination campaigns.

The last two chapters present a number of models for meningococcal B infection in New Zealand, and the effect of the recent nation-wide vaccination campaign. New Zealand has been experiencing an epidemic of meningococcal B disease since mid-1991, with a peak of 370 cases in 2001. The vaccination campaign initiated in 2004 was aimed at people aged less than 20 years old, in the hope of ending the epidemic. In Chapter Six we give a literature review of meningococcal models, although none have been used to look specifically at the New Zealand epidemic strain. We then develop a non-age-structured susceptible-carrier-infected-removed differential equation model, which is subsequently structured to include age dependent parameters and compared with the known yearly incidence of infection.

Chapter Seven then gives some alternative models for meningococcal B disease by considering the possibility that a person can be immune for a limited period of time. We explore different routes by which a person can be re-infected: return to the susceptible state after acute infection and carriage, with no immune class; immunity for those who have had the acute infection with carriers returning to the susceptible class; and a model that allows temporary immunity after both carriage and acute infection. The model with temporary immunity gives us the best fit to the known yearly incidence of infection for all age groups before vaccination, so we include the effect of the vaccination programme in this model to help us predict what the future of the epidemic will be. From here, we explore the effect of different vaccination campaigns, and show how the current vaccination

campaign has decreased our predicted yearly incidence of infection.

Chapter 2

Vaccination Strategies

2.1 Introduction

Vaccination is one of the most cost-effective ways of combating infectious diseases. Although vaccination against many childhood infections is highly recommended by health professionals, it is not compulsory - so the choice of whether to be vaccinated or not is left to the individual (or carer/parent of the child[ren]). However, the choice to be vaccinated not only affects the protection of the individual against the infection, but also the immunity of the entire community through "herd immunity".

In New Zealand, as well as the rest of the world, there are a number of groups and individuals who are against immunisation[1], who are concerned about issues such as the adverse side effects and efficiency of the vaccine and hold the opinion that natural immunity is better than imposed immunity. Hamilton *et al.* (2004) found that the majority of parents that chose not to immunise their child[ren] did so due to concerns about the risk of side-effects and complications from immunisations. Such concerns are compounded by media articles: in 1997 the measles-mumps-rubella (MMR) vaccine coverage declined in New Zealand (Mansoor *et al.*, 1998) after a possible linkage between the vaccination and Crohn's disease[2] (Thompson *et al.*, 1995) was announced in the media (and later discredited Feeney *et al.* (1997)). Yet Mansoor & Pillans (1997) state that the most frequently reported adverse side effect to the MMR vaccination in New Zealand is a rash, reported in 17 out of 100,000 doses. Wakefield *et al.* (1998) claimed there was a link between the MMR vaccination and autism in children. This was later retracted (Murch *et al.*, 2004) by most of the authors, and a later study found no such link (Smeeth *et al.*, 2004).

When deciding on whether to be vaccinated, the relative "costs" of the benefits and drawbacks of the vaccination both need to be considered. Suppose that there is an

[1] An example of such a group in New Zealand is the Immunisation Awareness Society (http://www.ias.org.nz/).

[2] Crohn's disease in an inflammatory disease of the digestive system which can cause abdominal pain, diarrhoea, vomiting and weight loss, of which there is no known drug or surgical cure.

expected cost associated with being vaccinated, C_V (Bauch *et al.*, 2003). This expected cost takes into account all the possible "costs": the monetary cost of the vaccine, the possible side effects that vaccination may cause and the time it takes to be vaccinated. With some vaccines this cost may be quite low, but with others it can be very high. The smallpox vaccination, for example, causes 1-2 deaths per million vaccinations (World Health Organisation, 2004). There is also an expected cost associated with being infected, C_I. This expected cost takes into account the effects of the infection, the monetary cost of treatment, the time required off work for recovery and any lasting side effects that may occur from the infection (for example scars from chicken pox, or the loss of limbs from meningitis). These two costs can be seen in purely monetary terms, as is used when calculating insurance rates. For the following calculations, it is assumed that C_V and C_I are both constant.

Assume that individuals can choose from the two options: remaining susceptible and risking being infected, or being vaccinated. The expected cost for the individual of remaining susceptible depends on the proportion of people in the population who are vaccinated, as this affects their chance of being infected. The individual will choose the option they perceive to present the lowest expected cost to them. However, the expected cost to the community as a whole also depends on the proportion of individuals choosing each strategy and the cost associated with each strategy. We assume that everyone in the population has access to the same information regarding the risks of being vaccinated and being infected, and that everyone perceives this information in the same manner.

We will now consider two different vaccination scenarios. The first is in response to an infection that requires a yearly vaccination, such as influenza, where we assume that the previous year's vaccination has had no lasting effect, and at the beginning of each year the entire population is once again susceptible to infection (Andreasen (2003) explores the case when different strains of influenza are present in the population each year). The second scenario is in response to an infection that is endemic in the population but has low prevalence, for which the vaccination is effective over a lifetime, such as tuberculosis. We will establish the proportion of the population that should be vaccinated in order to minimize the cost to the community as a whole, and compare this with the optimal solution for the individual.

The models used in this chapter will be used and extended in later chapters that involve more detailed models of the epidemiology of particular infections, where this chapter serves more as an (almost) infection independent analysis of the best vaccination strategies for individuals and the community.

2.2 Yearly Epidemics

Consider an infection, such as influenza, where individuals need to be vaccinated every year in order to be protected against infection. We require some preliminary calculations

regarding the infection before we look at the expected costs to the community and individuals. These calculations will be in terms of the proportion of the population that is vaccinated.

2.2.1 Background

Recall that if the basic reproduction ratio, R_0, is less than one then we know that on average one infected person will infect less than one other person, so an epidemic will not occur. Conversely, if $R_0 > 1$ we know that there will be an epidemic. Suppose that a proportion v of the population has been vaccinated at birth (or close to birth), by way of injection, mouth or other means, or they are naturally immune from the infection. Then, by definition of R_0, if

$$\begin{aligned} R_0(1-v) &> 1 \\ v &< 1 - \frac{1}{R_0} \end{aligned} \tag{2.1}$$

there will be an epidemic.

We can calculate R_0 from:

$$R_0 = N \int_0^\infty p(t)C(t)dt \tag{2.2}$$

where N is the total number of people in the population and $p(t)$ is the probability of infection given contact with an infective at time t after they were infected. $C(t)$ is the contact/mixing rate between a susceptible and an infective (Diekmann & Heesterbeek, 2000), which may depend on the time since the infectives were themselves infected.

At time t, the rate of new cases of infection (the incidence of infection, $i(t)$) depends on the contacts between susceptibles and infectives. We have:

$$i(t) = i(0)\delta(t) + S(t) \int_0^t p(\tau)C(\tau)i(t-\tau)d\tau \tag{2.3}$$

where $i(0)\delta(t)$ accounts for the number of initial cases of the infection in the population ($\delta(t)$ is the Dirac delta function), and $S(t)$ is the number of the population who are susceptible to infection at time t. For our simulations we have assumed that there is only one initial case of infection in the population.

The incidence of infection is equal to the negative rate of change in the susceptible population. Thus, we may rewrite Equation (2.3) as:

$$-\frac{dS(t)}{dt} = i(0)\delta(t) + S(t) \int_0^t p(\tau)C(\tau) \left[-\frac{dS(t-\tau)}{dt} \right] d\tau \tag{2.4}$$

To calculate the final size of the epidemic[3] we assume $t > 0$, and exclude the initial introduction of the infection in the population. We can then integrate with respect to

[3]This is based on the theory given in (Diekmann & Heesterbeek, 2000)

time to gain:

$$\int_{S(0)}^{S(\infty)} \frac{1}{S(t)} dS(t) = \int_0^\infty \int_0^t p(\tau)C(\tau)\frac{dS(t-\tau)}{dt} d\tau dt \tag{2.5}$$

By changing the order of integration we gain:

$$\int_{S(0)}^{S(\infty)} \frac{1}{S(t)} dS(t) = \int_0^\infty \int_\tau^\infty p(\tau)C(\tau)\frac{dS(t-\tau)}{dt} dt d\tau \tag{2.6}$$

Calculating the integral gives:

$$\log\left(\frac{S(\infty)}{S(0)}\right) = [S(\infty) - S(0)] \int_0^\infty p(\tau)C(\tau)d\tau \tag{2.7}$$

We can re-write Equation (2.7) in terms of proportions of the population by letting $s(\infty) = \frac{S(\infty)}{N}$ and $s(0) = \frac{S(0)}{N}$, giving:

$$\begin{aligned} \log\left(\frac{s(\infty)}{s(0)}\right) &= \left[\frac{s(\infty)}{s(0)} - 1\right] s(0)N \int_0^\infty p(\tau)C(\tau)d\tau \\ \log\left(\frac{s(\infty)}{s(0)}\right) &= \left[\frac{s(\infty)}{s(0)} - 1\right] s(0)R_0 \end{aligned} \tag{2.8}$$

From the above we see that that final size of an epidemic depends only on the basic reproduction ratio and the initial proportion of susceptibles in the population. Assuming that the basic reproduction ratio is set initially, we define a new reproduction ratio under vaccination, R_v, such that:

$$R_v = (1 - v)R_0 \tag{2.9}$$

Initially, we assume $s(0) = 1 - v$. Substituting this into Equation (2.8) gives:

$$\log\left(\frac{s(\infty)}{1-v}\right) = \left(\frac{s(\infty)}{1-v} - 1\right) R_v \tag{2.10}$$

We can calculate the proportion of the population that will still be susceptible after a disease outbreak has finished from the above equation[4]. If $R_v < 1$, then there will not be an epidemic, and the proportion of susceptibles in the population will remain unchanged, $s(\infty) = 1 - v$, and Equation (2.10) will not need to be solved. If $R_v > 1$ we can solve Equation (2.10) to find the solution $s(\infty) \neq 1 - v$.

To prove the existence of solutions to Equation (2.10) we let $z = \frac{s(\infty)}{1-v}$ and define $f(z) = \log z - R_v(z - 1)$, and now search for the roots of $f(z)$. As shown in Figure 2.1, we have two cases to consider: when $R_v > 1$ and when $R_v < 1$. From it's definition:

$$\begin{aligned} f'(z) &= \frac{1}{z} - R_v, \quad \text{and} \\ f''(z) &= -\frac{1}{z^2} \end{aligned}$$

As the second derivative is concave down for all positive values of z, we know $f(z)$ has at most two roots, one of which is located at $z = 1$. When $R_z < 1$, $f(z)$ will be decreasing at

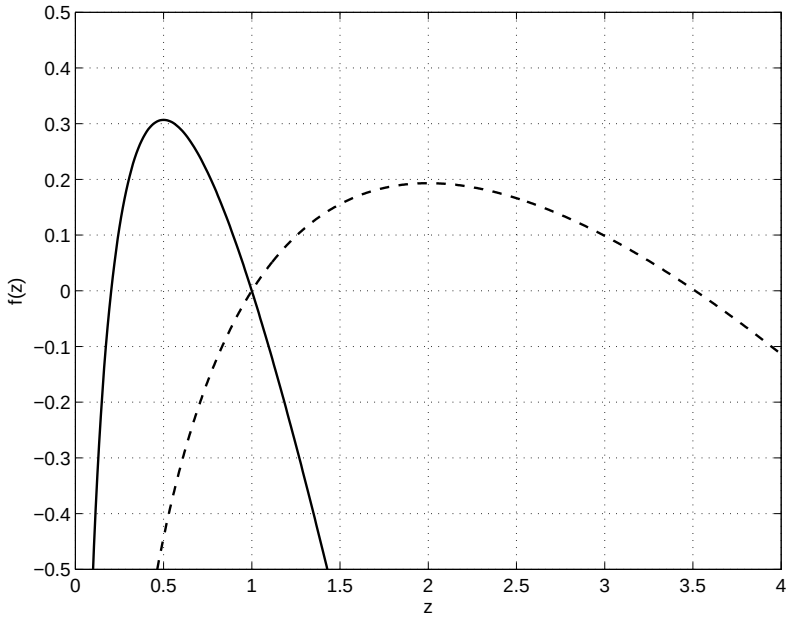


Figure 2.1: Plotting $f(z) = \log z - R_v(z-1)$ for two values of R_v: the solid line for $R_v = 2$ and the dashed line for $R_v = 0.5$. When $R_v < 1$ there is only one root in the range $0 < z < 1$, and when $R_v > 1$, there is a root in the range $0 < z < 1$.

some point when $z > 1$, thus a second root is located in the range $1 < z < \infty$. If $R_v > 1$, $f(z)$ will be decreasing when $z < 1$, so the second roots lies in the range $0 < z < 1$.

We know that $0 < s(\infty) < 1$ and we also need to establish that $s(\infty) < \frac{1}{R_0}$. To do this, we consider Equation (2.10) in exponential form, substituting $z = \frac{s(\infty)}{1-v}$:

$$z = e^{R_v(z-1)} \tag{2.11}$$

This relationship is illustrated in Figure 2.2. If we let $q(z) = e^{R_v(z-1)}$, then $q'(z) = R_v e^{R_v(z-1)} = R_v q(z)$. We know that $p(z) = z$ intersects $q(z)$ at $z = 1$ and at second point when $z < 1$ and $q'(z) < 1$. The intersection at $z = 1$ corresponds to the trivial case where there is no epidemic – we are interested in the case where $z < 1$ corresponding to an epidemic:

$$\begin{array}{rcl} & q'(z) & < & 1 \\ \Rightarrow & R_v e^{R_v(z-1)} & < & 1 \\ \Rightarrow & R_v z & < & 1 \\ \Rightarrow & z & < & \frac{1}{R_v} \\ \Rightarrow & s(\infty) & < & \frac{1}{R_0} \end{array} \tag{2.12}$$

We can see in Figure (2.3), $s(\infty)$ appears to reach a maximum when $v = 1 - \frac{1}{R_0}$. To verify this we consider the derivative of Equation (2.10) with respect to v:

$$\frac{ds(\infty)}{dv} = \frac{s(\infty)(R_0(1-v)-1)}{(1-v)(1-R_0 s(\infty))} \tag{2.13}$$

[4] A derivation of the final size equation using an SIR model is given in the Appendix.

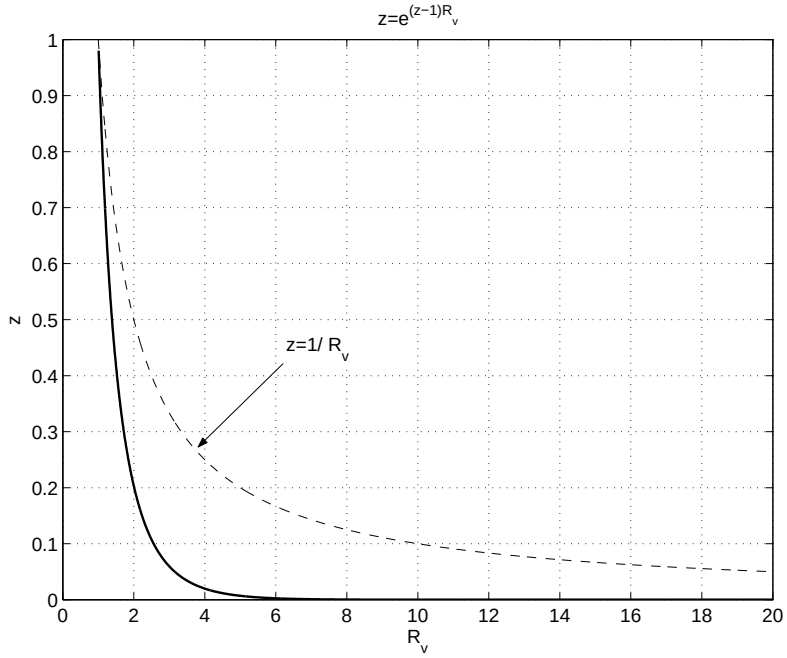


Figure 2.2: We can use Equation (2.11) to calculate the ratio z given any value for R_v. Note that it can be clearly seen that the dashed line representing $z = \frac{1}{R_v}$ is always greater than the solution to the equation.

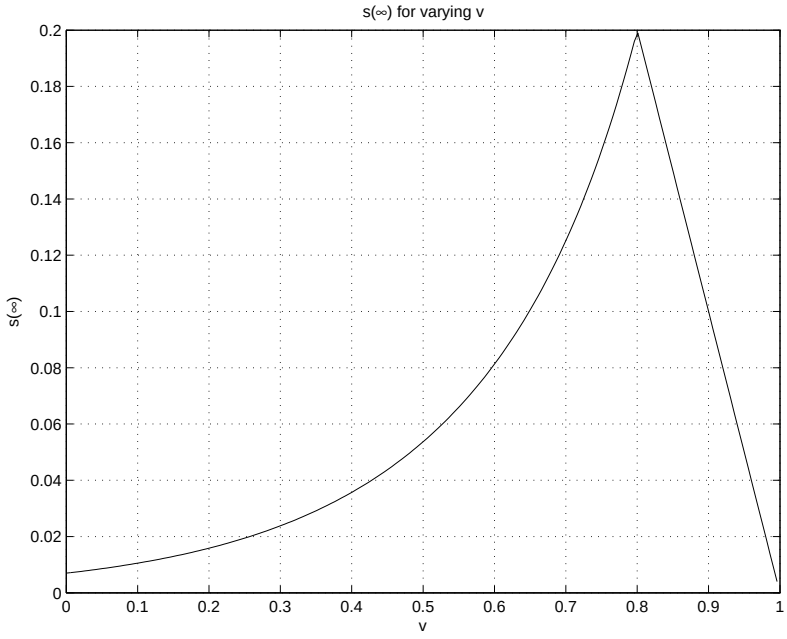


Figure 2.3: We can use Equation (2.10) to calculate $s_v(\infty)$ for any given value of v - where $s_v(\infty)$ is the proportion of the population that are susceptible after an epidemic. For this example we have $R_0 = 5$. Note that when $v > 1 - \frac{1}{R_0}$ (0.8 in this example), there is no epidemic (then $s_v(\infty) = 1 - v$).

As this function is only valid in the range $v \in \left[0, 1 - \frac{1}{R_0}\right]$ we know $R_0(1-v) - 1 > 0$ (as $R_0 > 1$), and we know $s(\infty)$, $(1-v)$, R_0 and $(1 - R_0 s(\infty))$ are all positive, so the above is an increasing function. When $v \in \left(1 - \frac{1}{R_0}, 1\right]$ we have $s(\infty) = 1 - v$ (a decreasing function), thus the maximum $s(\infty)$ is reached when $v = 1 - \frac{1}{R_0}$.

Substituting $v = 1 - \frac{1}{R_0}$ into Equation (2.10) yields:

$$\log\left(s(\infty)R_0\right) = s(\infty)R_0 - 1 \tag{2.14}$$

which has only one solution: $s(\infty)R_0 = 1$, that is $s(\infty) = \frac{1}{R_0}$.

Thus the maximum proportion of susceptibles remaining after an epidemic is $s(\infty) = \frac{1}{R_0}$ and is achieved when the proportion of the population equal to $v = 1 - \frac{1}{R_0}$ has been vaccinated. The proportion $v = 1 - \frac{1}{R_0}$ is the minimum proportion of the population that is required to be vaccinated in order to reduce the basic reproduction ratio below one. Ideally, a larger proportion of the population would need to be vaccinated in order to guarantee that there would be no more epidemics. If R_0 is close to one, there is likely to still be a few cases of infection, and stochastic fade out would occur, where there may be a few small outbreaks of infection before the infection is finally removed from the population.

2.2.2 Individual and Community Expected Costs

We let the cost associated with being vaccinated, C_V, and the cost associated with being infected, C_I, be constant. If v is the proportion of the population who are vaccinated, then the expected cost for individuals choosing to be vaccinated or not to be vaccinated (respectively) are:

$$\begin{aligned} E_v^Y &= C_V \\ E_s^Y &= \frac{1 - v - s(\infty)}{1 - v} C_I \end{aligned} \tag{2.15}$$

(where the superscript denotes we are dealing with yearly vaccination).

As $1 - v - s(\infty)$ is the proportion of the population who are infected after an epidemic, $\frac{1-v-s(\infty)}{1-v}$ is the probability that a non-vaccinated individual will be infected during an epidemic.

The expected cost to the whole community will be a linear combination of the expected costs of the two individual strategies:

$$\begin{aligned} C^Y(v) &= vC_V + (1-v)\frac{1 - v - s(\infty)}{1 - v} C_I \\ &= vC_V + (1 - v - s(\infty))C_I \end{aligned} \tag{2.16}$$

However, this only applies in the range $v \in \left[0, 1 - \frac{1}{R_0}\right]$, as if v is outside this range we know an epidemic will not occur (from Equation (2.1)), so we will only have to consider

the cost associated with vaccination. Thus:

$$C^Y(v) = \begin{cases} vC_V + (1 - v - s(\infty))C_I & \text{if } 0 \leq v \leq 1 - \frac{1}{R_0} \\ vC_V & \text{if } 1 - \frac{1}{R_0} < v \leq 1 \end{cases} \tag{2.17}$$

2.2.3 What Proportion of the Population should be Vaccinated?

We will calculate the proportion of the population that needs to be vaccinated to minimise the expected costs to individuals and the community.

For an individual, the lowest expected cost will either be C_V (the expected cost associated with being vaccinated) or $\frac{1-v-s(\infty)}{1-v}C_I$ (the expected cost associated with being infected) which depends on the proportion of the population that is vaccinated, v.

The individual's two strategies will be equal when:

$$\begin{aligned} E_v^Y &= E_s^Y \\ (1-v)C_V &= (1 - v - s(\infty))C_I \\ (1-v)\left(\frac{C_V}{C_I} - 1\right) &= -s(\infty) \\ v &= 1 - \frac{s(\infty)}{1 - \frac{C_V}{C_I}} \end{aligned} \tag{2.18}$$

where $s(\infty)(\neq 1)$ is the solution to Equation (2.10). This point is only valid in the range $v \in \left(0, 1 - \frac{1}{R_0}\right)$, as when v is outside this range there is only the cost associated with being vaccinated to consider. If the cost associated with being vaccinated is less than the cost associated with being infected, then

$$v = 1 - \frac{s(\infty)}{1 - \frac{C_V}{C_I}} \tag{2.19}$$

We know that $v = 1 - \frac{s(\infty)}{1-\frac{C_V}{C_I}} < 1 - \frac{1}{R_0}$, as the individuals expected cost of remaining susceptible goes to zero as v approaches $1 - \frac{1}{R_0}$ (as E_s^Y is a decreasing function in v). So the individuals two strategies must be equal at some point $v < 1 - \frac{1}{R_0}$.

If the cost associated with being vaccinated is zero, the break even point between the two costs will be at $v = 1 - s(\infty)$. As shown previously, this will be at its minimum when $s(\infty) = \frac{1}{R_0}$. Hence, when $C_V = 0$ the individual's break even point occurs when:

$$v = 1 - \frac{1}{R_0} \tag{2.20}$$

For the community, we need to minimise the community's cost function over v to find the proportion of the population that needs to be vaccinated. Differentiating Equation (2.17) with respect to v yields:

$$\frac{dC^Y(v)}{dv} = \begin{cases} C_V - (1 + \frac{ds(\infty)}{dv})C_I & \text{if } 0 < v < 1 - \frac{1}{R_0} \\ C_V & \text{if } 1 - \frac{1}{R_0} < v < 1 \end{cases} \tag{2.21}$$

recalling

$$\frac{ds(\infty)}{dv} = \frac{s(\infty)(R_0(1-v)-1)}{(1-v)(1-R_0 s(\infty))} \tag{2.22}$$

from Equation (2.13), and remembering that $R_v = (1-v)R_0$. This gives:

$$\frac{dC^Y(v)}{dv} = \begin{cases} C_V - \left(1 + \frac{s(\infty)(R_0(1-v)-1)}{(1-v)(1-R_0 s(\infty))}\right) C_I & \text{if } 0 < v < 1 - \frac{1}{R_0} \\ C_V & \text{if } 1 - \frac{1}{R_0} < v < 1 \end{cases} \tag{2.23}$$

In the range $v \in \left(1 - \frac{1}{R_0}, 1\right)$ there are no critical points unless the cost associated with vaccination is zero.

In the range $v \in \left(0, 1 - \frac{1}{R_0}\right)$ a critical point occurs when:

$$\begin{aligned} \frac{C_V}{C_I} - 1 &= \frac{s(\infty)(R_0(1-v)-1)}{(1-v)(1-R_0 s(\infty))} \\ v &= \frac{C_V(1-R_0 s(\infty)) - C_I(1-s(\infty))}{C_V(1-R_0 s(\infty)) - C_I} \end{aligned} \tag{2.24}$$

For the above relation to hold, we need $\frac{C_V}{C_I} > 1$ – that is, the cost associated with vaccination is greater than the cost associated with being infected. If this were the case, the vaccination would probably not be available to the population, so we say that this is not a feasible scenario (the mathematical exploration of this case is left to the Appendix).

If the cost associated with vaccination is less than the cost associated with being vaccinated, we can see that $C^Y(v)$ is a decreasing function (in v) if $v \in \left(0, 1 - \frac{1}{R_0}\right)$, then an increasing function when $v \in \left(1 - \frac{1}{R_0}, 1\right)$. Thus, the minimum expected cost to the community is achieved when:

$$v = 1 - \frac{1}{R_0} \tag{2.25}$$

As a special case, if the cost associated with vaccination is zero, then from Equation (2.17), we see that the cost to the community will be zero when $v \in \left(1 - \frac{1}{R_0}, 1\right)$, and will be decreasing when $v \in \left(0, 1 - \frac{1}{R_0}\right)$. Thus the minimum cost to the community is achieved when:

$$v \geq 1 - \frac{1}{R_0} \tag{2.26}$$

An example of the relationship between the two individual expected costs and the community's expected cost is shown in Figure 2.4 which clearly shows the individuals "break even" point is before the minimum cost for the community where $C_V < C_I$. An example of the situation where $C_V = 0$ is shown in Figure 2.5. A summary of all the results from this section is given in Table 2.1.

The distance between the individual's break even point and $v = 1 - \frac{1}{R_0}$ depends on the ratio of the cost associated with vaccination and with being infected. We let

$$v_i^* = 1 - \frac{s(\infty)}{1 - \frac{C_V}{C_I}} \tag{2.27}$$

	$0 < C_V < C_I$		$C_V = 0$	
	v value	Expected Cost	v value	Expected Cost
Individual's Strategies Equal	$1 - \frac{s(\infty)}{1-\frac{C_V}{C_I}}$	C_V	$1 - \frac{1}{R_0}$	0
Community Cost at its Minimum	$1 - \frac{1}{R_0}$	$\left(1 - \frac{1}{R_0}\right) C_V$	$\geq 1 - \frac{1}{R_0}$	0

Table 2.1: Table to summarise the proportion of the population that needs to be vaccinated in order to minimise the expected cost to the community and when the two individual strategies are equal, and the associated expected cost.

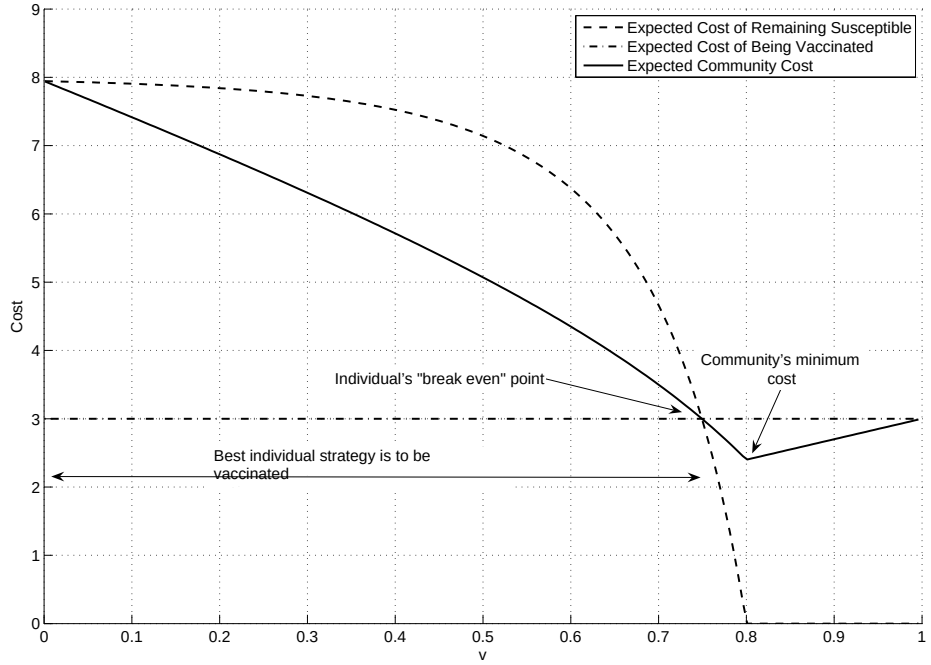


Figure 2.4: When the expected cost of remaining susceptible is greater than the cost of being vaccinated, we can see that the individual's best strategy is to be vaccinated, until v reaches v^*_{ind} – the break even point between the individual's strategies (where all three lines intersect), then their best strategy is to remain susceptible. The best strategy for the community is to vaccinate the proportion of the population equal to $1 - \frac{1}{R_v}$ – which is greater than the individual's best strategy. $R_0 = 5$, $C_v = 3$ and $C_i = 8$ for this example.

and

$$v^*_c = 1 - \frac{1}{R_0} \tag{2.28}$$

Then plotting $v^*_c - v^*_i$ (as shown in Figure 2.6) as a function of $\frac{C_V}{C_I}$ we can see that as the ratio of the two costs increases towards one, the difference tends towards $1 - \frac{1}{R_0}$.

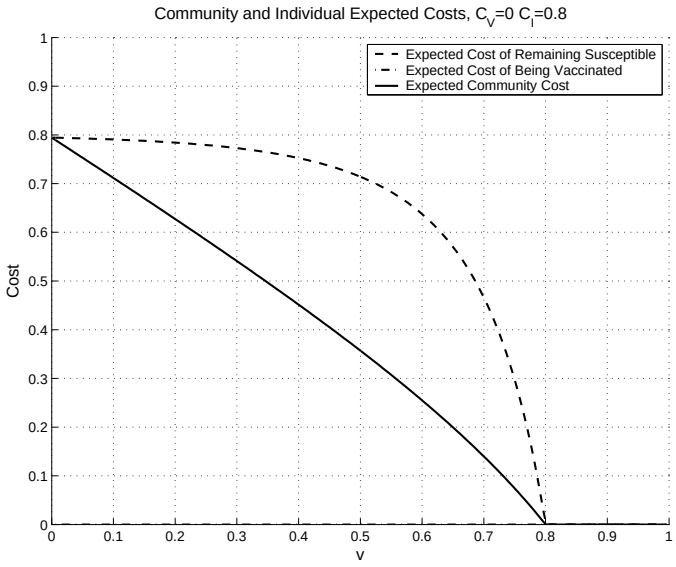


Figure 2.5: When the cost associated with being vaccinated is zero, the break even point between the two individual strategies and the minimum cost to the community occur when $v = 1 - \frac{1}{R_0}$. For this example, $R_0 = 5$.

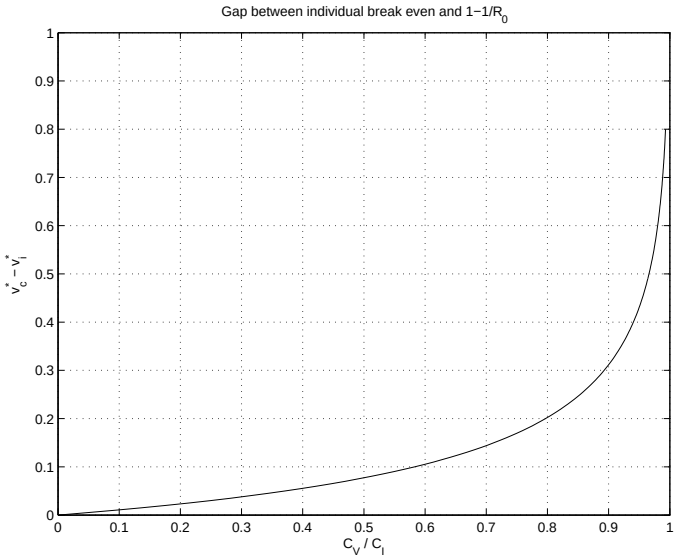


Figure 2.6: The distance between v_c^* and v_i^* as a function of the ratio of the two costs, where $R_0 = 5$.

Vaccine (number of doses)	*Vaccine Efficacy*	*Duration of immunity after primary series*
BCG [a] (1)	$0\% - 80\%$ for pulmonary tuberculosis, $75\% - 86\%$ for meningitis and miliary TB	Unknown; some evidence that immunity wanes with time
Diphtheria toxios (3)	$> 87\%$ (no data from developing countries)	Variable: probably around 5 years; longer in presence of natural boosting or booster doses
Tetanus toxoid (3)	$> 95\%$ ($> 80\%$ after two doses) in infants	five years
Pertussis (3)	Estimates vary widely because the products vary; efficacy higher against severe disease (in most instances at least 80% protection against severe disease)	Unknown; some evidence that it wanes with time
Polio (3)	$> 90\%$ in industrialised countries; $72\% - 98\%$ in hot climates; lower protection against type 3	Lifelong if boosted by wild virus; may be shorter when no wild virus circulating
Measles (1)	$> 90\%$ at 12 months of age $> 85\%$ at 9 months of age	Lifelong if boosted by wild virus; may be shorter when no wild virus circulating
Hib [b] (3)	$> 95\%$ for invasive disease	Unknown but lasts for at least 3 years beyond period of greatest exposure
Hepatitis B (3)	$75\% - 95\%$ efficacy against chronic infection	> 15 years; further follow-up continuing
Yellow fever (1)	$90\% - 98\%$	For at least several decades, possibly for life

Table 2.2: Vaccine duration after primary series of immunisation for some vaccine preventable infections. Values taken from (World Health Organisation, 2002)

[a] Bacillus Calmette-Guerin immunisation for Tuberculosis

[b] *Haemophilus influenzae* type b

2.3 Life-Long Vaccination

Now consider an infection, such as tuberculosis, for which one vaccination is sufficient to give immunity over a lifetime (New Zealand Ministry of Health, 2002) (see Table 2.2 for vaccine efficacy and duration for selected infections). We assume that if a person is vaccinated it is at birth or near to birth, and they are not included in the susceptible population prior to vaccination.

To calculate the proportion of the population that needs to be vaccinated in order to minimise the cost to the individual and to the community, we start by considering a susceptible, infected and removed (SIR) model for the infection.

2.3.1 SIR Model

We let $S(t)$, $I(t)$ and $R(t)$ denote the number of the population that are susceptible, infectious and removed/immune, respectively, in relation to the infection. We can express the relationship between the rate of change in these three classes by the following model, where the population size is constant, N:

$$\begin{aligned} \frac{dS}{dt} &= \mu(1-v)N - \beta SI - \mu S && (2.29)\\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I && (2.30)\\ \frac{dR}{dt} &= \gamma I - \mu R + \mu v N && (2.31) \end{aligned}$$

where v is the proportion of the population who have been vaccinated at birth[5], so are not susceptible to the infection. The birth and death rate, μ, is held constant to maintain a constant population size, γ is the rate at which infectives recover, and β is the transmission coefficient. As the population size is constant ($S+I+R=N$), one of the above equations is redundant – we shall omit the $\frac{dR}{dt}$ equation in later calculations.

We can then non-dimensionalise Equations (2.29)–(2.31) by letting $s = \frac{S}{N}$, $i = \frac{I}{N}$, $r = \frac{R}{N}$, and $\tau = \gamma t$. If we let $\frac{\mu}{\gamma} = \epsilon$, Equations (2.29)–(2.31) become[6]:

$$\begin{aligned} \frac{ds}{d\tau} &= \epsilon(1-v) - (R_0(1+\epsilon)i + 1)s \\ \frac{di}{d\tau} &= (1+\epsilon)\left(R_0 s - 1\right) i \\ \frac{dr}{d\tau} &= i - \epsilon(r - v) && (2.32) \end{aligned}$$

where the basic reproduction ratio for the system is given by $R_0 = \frac{\beta N}{\gamma(1+\epsilon)}$ (Anderson & May, 1992).

[5] At birth means the entry class into the susceptible population - as we will be starting our simulations from age 6 months.

[6] note that i is now representing the proportion of the population who are infected, as opposed to the incidence of infection.

There are two steady states for the above system (found by setting the left hand side of each equation to zero and solving): the trivial steady state $(s^*, i^*) = (1 - v, 0)$, so everyone who is not vaccinated is susceptible to the infection and no one is infective.

The endemic steady state of the system, where the infection is always present is:

$$(s^*, i^*) = \left(R_0^{-1}, \frac{\epsilon(R_0(1-v)-1)}{R_0(1+\epsilon)} \right) \tag{2.33}$$

This is a well known result and is shown in Anderson & May (1992) and Diekmann & Heesterbeek (2000), who demonstrate that this is a stable steady state solution.

2.3.2 Individual and Community Expected Costs

If the proportion of the population susceptible and infected is held at steady state value, the chance that a person will be infected at some point during their lifetime is given by:

$$\text{Prob(infection during lifetime)} = \frac{R_0(1+\epsilon)i^*}{R_0(1+\epsilon)i^* + \epsilon} \tag{2.34}$$

Substituting in our value for i^* from the endemic steady state, Equation (2.33), we have:

$$\text{Prob(infection during lifetime)} = 1 - \frac{1}{R_0(1-v)} \tag{2.35}$$

If we let the basic reproduction ratio under vaccination be defined as $R_v = (1-v)R_0$, we can re-write the probability of being infected during a lifetime as:

$$\text{Prob(infection during lifetime)} = 1 - \frac{1}{R_v} \tag{2.36}$$

We may now calculate the expected costs for individuals and the community for remaining susceptible and for being vaccinated. Assume that there is a constant cost associated with being vaccinated, C_V, and a constant cost associated with being infected, C_I. An individual in the population can decided whether to remain susceptible or be vaccinated (at birth or close to birth), then the expected cost for each of these strategies, respectively, is:

$$\begin{aligned} E_v^L &= C_V \\ E_s^L &= \left(1 - \frac{1}{R_v}\right) C_I \end{aligned} \tag{2.37}$$

The expected cost to the community will be a combination of the above two individual strategies:

$$\begin{aligned} C^L(v) &= vC_V + (1-v)(1 - \frac{1}{R_v})C_I \\ &= vC_V + \left((1-v) - \frac{1}{R_0}\right) C_I \end{aligned} \tag{2.38}$$

Again, we know that the infection will be prevented when $v > 1 - \frac{1}{R_0}$, so we can write the expected community cost as a piecewise continuous function:

$$C^L(v) = \begin{cases} vC_V + \left(\left(1 - \frac{1}{R_0}\right) - v\right) C_I & \text{if } 0 < v < 1 - \frac{1}{R_0} \\ vC_V & \text{if } 1 - \frac{1}{R_0} < v < 1 \end{cases} \tag{2.39}$$

2.3.3 What Proportion will Minimise the Costs?

For an individual, there is a point when the expected costs of remaining susceptible and being vaccinated are equal, that is:

$$\begin{aligned} E_v^L &= E_s^L \\ C_V &= \left(1 - \frac{1}{R_0(1-v)}\right) C_I \\ v &= 1 - \frac{1}{R_0\left(1 - \frac{C_V}{C_I}\right)} \end{aligned} \tag{2.40}$$

This is only feasible when the cost associated with being infected is greater than the cost of being vaccinated. We can also see that this break even point occurs when $v < 1 - \frac{1}{R_0}$.

To find the proportion of the population that needs to be vaccinated in order to minimise the expected cost to the community, we calculate the derivative of Equation (2.39):

$$\frac{dC^L(v)}{dv} = \begin{cases} C_V - C_I & \text{if } 0 < v < 1 - \frac{1}{R_0} \\ C_V & \text{if } 1 - \frac{1}{R_0} < v < 1 \end{cases} \tag{2.41}$$

As a special case, if the cost associated with being vaccinated is zero (as shown in Figure 2.8), then the lowest cost to the community will be achieved whenever

$$v \geq 1 - \frac{1}{R_0} \tag{2.42}$$

When the cost associated with vaccination is less than the cost associated with being infected, we can see that the community's expected cost is a decreasing function of v when $0 < v < 1 - \frac{1}{R_0}$ and an increasing function when $1 - \frac{1}{R_0} < v < 1$ (as example of this is shown in Figure 2.7. So the minimum expected cost to the community will occur when

$$v = 1 - \frac{1}{R_0} \tag{2.43}$$

If we now let

$$v_i^* = 1 - \frac{1}{R_0\left(1 - \frac{C_V}{C_I}\right)} \tag{2.44}$$

and

$$v_c^* = 1 - \frac{1}{R_0} \tag{2.45}$$

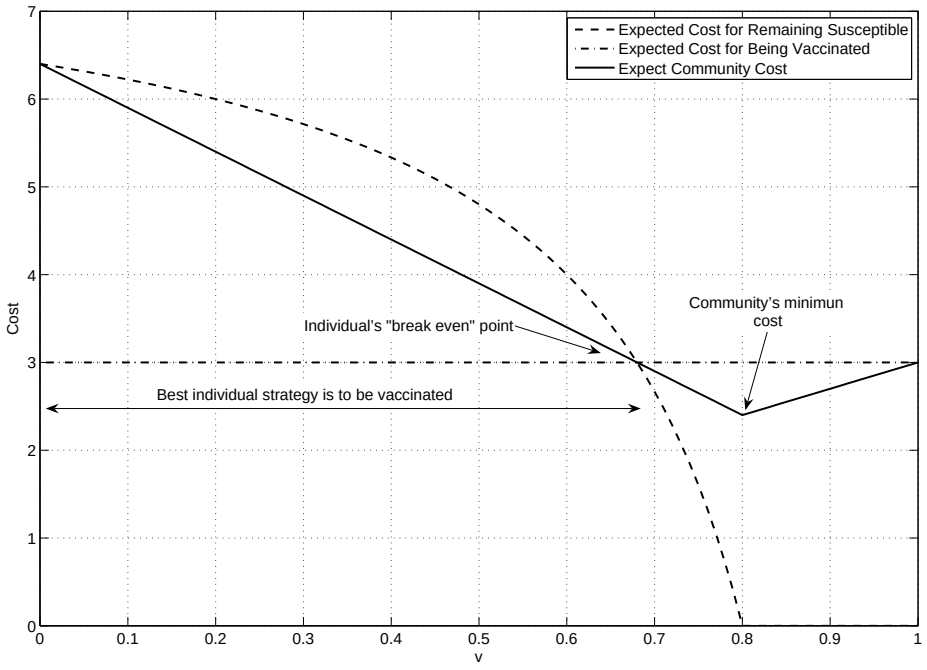


Figure 2.7: For this example $R_0 = 5$, so there is only an epidemic if $v < 1 - \frac{1}{R_0} = 0.8$. We can see that the lowest cost to the community occurs when $v = 1 - \frac{1}{R_0}$, and the individual equilibrium occurs at a point v^*_{ind} less than $v = 1 - \frac{1}{R_0}$. $C_v = 3$ and $C_i = 8$.

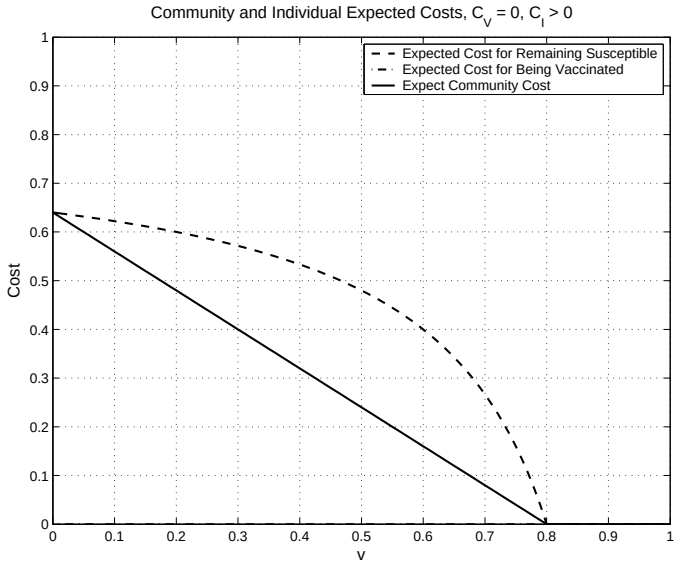


Figure 2.8: When the cost associated with being vaccinated is zero, the minimum cost to the community and the break even point between the two individual strategies are when $v = 1 - \frac{1}{R_0}$, and the corresponding expected cost is 0. For this plot $R_0 = 5$.

then the difference between the individuals' break even point and the minimum cost to the community is:

$$v_c^* - v_i^* = \frac{\frac{C_V}{C_I}}{R_0\left(1 - \frac{C_V}{C_I}\right)} \tag{2.46}$$

When $C_V < C_I$, the individual's "break even" point occurs when the proportion of the population that is vaccinated is less than $1 - \frac{1}{R_0}$, and the community's minimum cost is at $v_c^* = 1 - \frac{1}{R_0}$. As the ratio C_v/C_I tends towards the community's minimum cost, the difference between the minimum cost to the community and the individual's "break even" point tends to $1 - \frac{1}{R_0}$. Thus, the largest difference between the best community and individual strategy is when $\frac{C_V}{C_I} \to 1 - \frac{1}{R_0}$ (depicted in Figure 2.9).

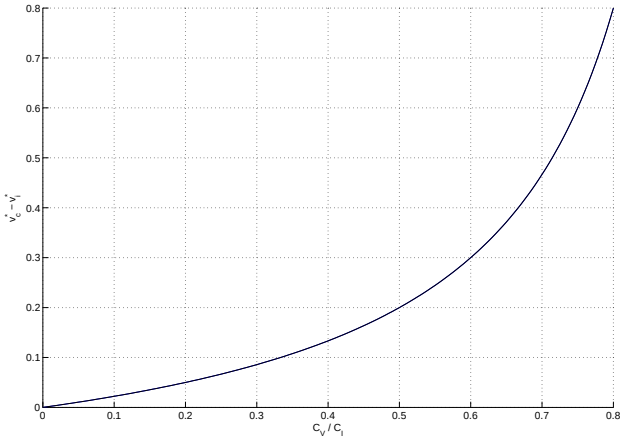


Figure 2.9: The difference between the individual's break even point and $1 - \frac{1}{R_0} = 0.8$ plotted as a function of the ratio of the costs associated with being vaccination and being infected, when $R_0 = 5$.

2.4 Discussion

When given a choice to be vaccinated, there are many different factors to consider. The two main factors are the relative costs associated with being vaccinated and being infected. If the expected cost associated with the vaccine is higher than the expected cost from actually having the infection, then the best option is to simply not be vaccinated. This strategy extends to the community as a whole – if the expected cost of being vaccinated is higher than the expected cost of the infection, then no one in the community should be vaccinated (as can be seen in Figures A.1 and A.2 in the Appendix). This is merely common sense, and we would hope that a vaccine such as this would not be marketed!

If the cost for being infected and being vaccinated are the same, then the break even point (for both yearly and lifelong vaccination) for individuals is for a proportion $1 - \frac{1}{R_0}$ of the population to be vaccinated. This is the same proportion of the population that

needs to be vaccinated in order for the expected cost to the community to be minimised. Examples of this can be seen in Figures (A.1) and (A.2).

Ideally, the cost of the vaccination should be lower than the cost of being infected. Then the best strategy for the community is to *always* vaccinate a proportion of the population equal to $1 - \frac{1}{R_0}$, as demonstrated in Figures (2.4) and (2.7). Note that this value depends only on the characteristics of the infection and not on either of the associated costs. From an individual's point of view, if the cost associated with being vaccinated is lower than the cost associated with remaining susceptible, as long as a large enough proportion of the population are vaccinated, they need not be vaccinated - which leads to a lower individual expected cost. This, again is common sense, as, if everyone you are in contact with is vaccinated against the infection (assuming that the vaccination inhibits the ability to carry and contract the disease), then there is little chance that you will be infected.

A break even point between the two individual's strategy choices (to vaccinate or not to vaccinate) is reached when the proportion of the population equal to $1 - \frac{s(\infty)C_I}{C_I - C_V}$ (where $s(\infty)$ is calculated from the non-linear Equation (2.10)) has been vaccinated in the case of yearly vaccination and when the proportion of the population equal to $1 - \frac{1}{R_0\left(1-\frac{C_V}{C_I}\right)}$ has been vaccinated for lifelong vaccination. Up to this break even point, the best strategy for the individual is to be vaccinated, but between this point and the the community's optimum at $v = 1 - \frac{1}{R_0}$, the lowest expected cost is achieved by remaining susceptible. This can be seen from Equations (2.15) and (2.37), by letting v increase toward $1 - \frac{1}{R_0}$. The same result has been shown by (Bauch & Earn, 2004), for the yearly epidemics from an individual's point of view, using game theory analysis.

When there is a perfect vaccination, in the sense that the cost associated with it is zero, in both the yearly and life long vaccination schedules, the best strategy for the community is to vaccinate a proportion of the population equal to $1 - \frac{1}{R_0}$. For the individuals, the best strategy will always be to be vaccinated, but the expected cost for both options will be equal when $v \geq 1 - \frac{1}{R_0}$.

If $s(\infty) = 1 - \frac{1}{R_0}$ in the yearly vaccination scenario, it becomes equivalent to the lifelong scenario in terms of the individuals break even point. However, for $s(\infty) = 1 - \frac{1}{R_0}$ in the yearly case, Equation (2.10) only has one solution $R_v = 1$, that is $v = 1 - \frac{1}{R_0}$ which makes the individuals and community's minimum costs coincide.

For both cases, yearly and lifelong vaccination schedules, the expected cost of remaining susceptible is equal to the cost of being infected multiplied by the probability of being infected (which depends on the proportion of the population that is vaccinated). So individuals either incur the full cost, or no cost at all associated with being infected - which may not be realistic for some infections, as there may be mild and severe cases of infection that should be reflected with different expected costs.

Bauch *et al.* (2003) presented a similar analysis considering the smallpox virus for which they used a differential equation model for the epidemic that had to be solved numerically. They found the individual break even point occurred when 19% of the

population was vaccinated, compared to 47% needed for the minimum cost to the community to be acheived. They then did a sensitivity analysis on their parameters (using a Monte Carlo method) and found that the average values for both the individual and community optimum proportions vaccinated always differed with $v_i^* < v_c^*$. Shortly after the work presented in this thesis was completed, Bauch *et al.* published a paper using an SIR epidemic model (Bauch & Earn, 2004) that could be solved analytically. They went on to analyse the changes in vaccine uptake given changes in the perceived risk of vaccination.

Both the integral equation model and the SIR model can be expanded to include a structured population - where the structure could be based on age, location or even socio-economic group. Further investigation can include making the cost associated with vaccination and remaining susceptible dependent on time, which was considered using a different method by Bauch *et al.* (2003), and iterating the yearly epidemics in a discrete map to explore the long term behaviour of the model.

2.5 Conclusion

We have shown that if the cost associated with being vaccinated is zero or less than the cost associated with being infected, the lowest expected cost to the community is reached when a proportion of the population equal to $1 - \frac{1}{R_0}$ has been vaccinated.

When the cost associated with vaccination is non-zero and less than the cost associated with remaining susceptible, the individual's lowest cost is achieved from vaccination when v is less than the break even point between the two strategies. When v is between the break even point and $1 - \frac{1}{R_0}$, the lowest cost to the individual is gained by remaining susceptible. However, if the cost associated with being vaccinated is zero, then, obviously, the lowest expected cost to the individual is achieved by being vaccinated - no matter what proportion of the population has already been vaccinated. In this case, the two strategies available to the individual will be equal when $v = 1 - \frac{1}{R_0}$ - when the lowest expected cost to the community is achieved.

If the cost associated with being infected and the cost associated with being vaccinated are the same, then the lowest cost to the community is still attained when $v = 1 - \frac{1}{R_0}$, but for the individuals, their two strategies will never be equal.

If the choice of being vaccinated is left to the individual, there is a chance that the community may suffer if a high enough proportion decides against vaccination. Conversely there is a chance that the individuals may endure a higher expected cost than necessary in order to minimise the cost to the community.

Chapter 3

Discrete Mapping for Repeated Measles Epidemics

3.1 Introduction

In 2003 there were more than half a million deaths worldwide caused by measles[1], the majority of these being deaths of children. The measles virus replicates in the cells at the back of the throat and lungs, and causes one of the most contagious diseases known, with almost all non-immunised children contracting the infection if they are exposed to it. However, children do not usually die directly from the infection, but rather from the complications caused by the infection (such as pneumonia and severe diarrhoea); complications are more common in children under 5 and adults over 20.

The initial signs of infection start 10 – 12 days after exposure and last for 1 – 7 days. Symptoms usually start with a high fever (for 1 – 7 days) then progress to a runny nose, cough, red and watering eyes and, finally, small white spots on the inside of the cheeks. Several days later a rash develops usually on the face and upper neck, which then spreads downwards to cover the rest of the body over a period of about three days, and persists for a further 5 – 6 days before fading. The virus can be transmitted by an infected individual from four days prior to the onset of the rash to four days after.

Immunisation against measles was introduced in New Zealand in 1969 for children between 10 months and five years of age who had not previously had measles, and for children aged under ten years who were deemed to be at special risk. The vaccination schedule was altered in 1974 and again in 1981 to finally result in the vaccine that was administered at 10 months old to be administered between 12 – 15 months of age. The measles vaccine was abolished in 1990 when the triple MMR (measles-mumps-rubella) was introduced and administered at 12 – 15 months of age (New Zealand Ministry of Health (2002)). In 1992 another scheduled vaccination for 11 years old was introduced, and in 1996 the first vaccination was given at 15 months of age.

[1] World Health Organisation: http://www.who.int/mediacentre/factsheets/fs286/en/

At this stage epidemics were still occurring every 5 – 6 years. In 1996 a mathematical model using a differential equations approach (Roberts and Tobias, 2002) successfully predicted an epidemic in 1997 and was a key factor in the decision to implement an intensive MMR vaccination campaign for children under 10 years of age, which was successful in preventing the epidemic. The model also went on to predict that with the then current vaccination schedule, another epidemic would occur in 2003 or 2004. This did not happen as the vaccination schedule was changed to give the first MMR vaccination at 15 months of age and the second vaccination at four years (New Zealand Ministry of Health (2003)), which increased coverage sufficiently high enough in the population to prevent further epidemics.

We have used an alternative approach to modelling the dynamics of epidemics by using integral equations to generate a discrete mapping that in turn generates the epidemic pattern. This allows us to separate out the two time scales that are present within the model, as the actual epidemic moves on a much faster time scale than the change in the population. An integral equation method is used to calculate the number of susceptibles who are infected during an epidemic, then a discrete map is developed by combining this with the change in the population demographics.

The incidence of new cases of infection depends on the history of the epidemic through an infection kernel rather than simply on the current susceptible and infected population sizes. This allows a general model to be easily reformulated for a specific infection by simply altering the kernel (details of the integral equation approach appear in Diekmann & Heesterbeek (2000)). While the rate of spread and the probability of disease transmission over the course of a year depend on this kernel, the total number of susceptibles infected during an epidemic depends only on the basic reproduction ratio.

3.2 An integral equation model

As measles tends to effect children more than adults, we will stratify our population into four age classes in relation to the infection: 6 – 15 months (group 1); 15 months – 5 years (group 2); 5 – 11 years (group 3) and 11 – 25 years (group 4). Infants under 6 months old are assumed to have protection from maternal antibodies, and those older than 25 years we deem not to be at risk of infection, so both of these age groups will not play a part in the epidemic process.

To find the number of people who are infected during the course of an epidemic (which will run during a one year time frame), we use the equation for incidence of infection:

$$i_j(t) = \delta(t) i_j(0) + S_j(t) \sum_{m=1}^{4} C_{jm} \int_0^t A_m(\tau) i_m(t-\tau) d\tau \tag{3.1}$$

for $j = \{1, 2, 3, 4\}$, where $i(t)$ is a 1×4 vector of the incidence of infection is each age category at time t noting that

$$i_l = -\frac{dS_l}{dt} \tag{3.2}$$

$S(t)$ is a 1×4 vector containing the number of susceptibles in each age category, $A(\tau)$ is also a 1×4 vector, representing the probability of being infected given contact with an infective (at time τ after they were themselves infected). C is a matrix describing the (constant) contact rates between each age group, where $\epsilon < 1$ is a parameter to weight the between-class contacts (we have used $\epsilon = 0.4$ for our simulations) – which implies that the mixing rates between classes is substantially smaller than the mixing within classes, as shown below. The values a_i in the contact matrix are seen as an activity level for each age group (we have used $\{a_1, a_2, a_3, a_4\} = \{1, 2, 6, 3\}$ for our simulations, see Roberts & Tobias (2000) for more details). We take a weighted geometric average of the activity levels to describe the contact between people in different age groups, but we do not weight the activity between contacts within the same age group.

$$C = \begin{pmatrix} a_1 & \epsilon\sqrt{a_1 a_2} & \epsilon\sqrt{a_1 a_3} & \epsilon\sqrt{a_1 a_4} \\ \epsilon\sqrt{a_1 a_2} & a_2 & \epsilon\sqrt{a_2 a_3} & \epsilon\sqrt{a_2 a_4} \\ \epsilon\sqrt{a_1 a_3} & \epsilon\sqrt{a_2 a_3} & a_3 & \epsilon\sqrt{a_3 a_4} \\ \epsilon\sqrt{a_1 a_4} & \epsilon\sqrt{a_2 a_4} & \epsilon\sqrt{a_3 a_4} & a_4 \end{pmatrix} \tag{3.3}$$

To measure the spread of an infection in a population we use the basic reproduction ratio, R_0, some examples of R_0 values for measles are given in Table 1.1. If $R_0 > 1$ then there is an epidemic, but if $R_0 < 1$ a few people may be infected, but the infection will not last in the population and there is no epidemic. For a multiple compartment model, we calculate R_0 from the next generation matrix, which can be thought of as a matrix with each component representing a basic reproduction ratio for each type of infection – for this model, the type of infection is the age group that the person belongs to. The entry $M_{i,j}$ is the number of secondary cases of infection in group i due to primary infection in group j. For example, the second entry on the third row will be the expected number of age group 3 infectives that are produced from an infectious person in age class 2. To determine the next generation matrix we first make the assumption that the probability of being infected given contact with an infective is the same for every age group, so $A_1 = A_2 = A_3 = A_4$. We let $\int_0^t A(\tau)d\tau = \tilde{A}$, so the next generation matrix is:

$$M = \tilde{A} \begin{pmatrix} a_1 S_1(0) & \epsilon\sqrt{a_1 a_2} S_1(0) & \epsilon\sqrt{a_1 a_3} S_1(0) & \epsilon\sqrt{a_1 a_4} S_1(0) \\ \epsilon\sqrt{a_1 a_2} S_2(0) & a_2 S_2(0) & \epsilon\sqrt{a_2 a_3} S_2(0) & \epsilon\sqrt{a_2 a_4} S_2(0) \\ \epsilon\sqrt{a_1 a_3} S_3(0) & \epsilon\sqrt{a_2 a_3} S_3(0) & a_3 S_3(0) & \epsilon\sqrt{a_3 a_4} S_3(0) \\ \epsilon\sqrt{a_1 a_4} S_4(0) & \epsilon\sqrt{a_2 a_4} S_4(0) & \epsilon\sqrt{a_3 a_4} S_4(0) & a_4 S_4(0) \end{pmatrix} \tag{3.4}$$

where $S_i(0)$ is the initial susceptible population in group i. The basic reproduction ratio for the system is the spectral radius (the largest eigenvalue) of the next generation matrix[2]:

$$R_0 = \rho\,(M) \tag{3.5}$$

The basic reproduction ratio for measles in New Zealand with no vaccination was estimated by Roberts & Tobias (2000) to be 12.8. As the contact rates and initial

[2]See Diekmann & Heesterbeek (2000) for more details on the calculation of R_0.

susceptible populations are known, so we can calculate

$$\tilde{A} = \frac{R_0}{\rho\left(\tilde{M}\right)} \tag{3.6}$$

where $\tilde{M} = M/\tilde{A}$.

Our model does not depend on the shape of each function $A_l(\tau)$, but only on the area under each function, which we have assumed to be the same for all age groups. However, the progression of the epidemic itself depends on the shape of the each function $A_l(\tau)$ which we have not explored.

To calculate the number of susceptibles remaining in the population after an epidemic ($S(\infty)$) we use the final size equation, which is gained by making the substitution of Equation (3.2) into Equation (3.1), and integrating:

$$\left(\log \frac{S_j(\infty)}{S_j(0)}\right) = \tilde{A} \sum_{m=1}^{4} C_{jm}(S_j(\infty) - S_j(0)) \tag{3.7}$$

Initially we set the populations of each age group to be proportional to the birthrate and the size of the age group:

$$\begin{aligned} S_1(0) &= B\frac{15-6}{12} \\ S_2(0) &= B\left(5 - \frac{15}{12}\right) \\ S_3(0) &= B\,(11-5) \\ S_4(0) &= B\,(25-11) \end{aligned} \tag{3.8}$$

where $B = 57435$ births per year – the live birth rate in 2004 (Statistics New Zealand (2004)).

The system of Equations (3.7) cannot be solved directly when ϵ is non-zero, so we expand $S_l(\infty)$ asymptotically in the small parameter ϵ (when $\epsilon = 0$ the system decouples to four separate equations which will not require asymptotic expansions to solve). That is:

$$S_j(\infty) = S_{j0} + \epsilon S_{j1} + \epsilon^2 S_{j2} + \epsilon^3 S_{j3} + \ldots \tag{3.9}$$

for $j = 1, 2, 3, 4$.

The full asymptotic expansion of our equations is:

$$\begin{pmatrix} \log\frac{S_{10}}{S_1(0)} + \frac{S_{11}}{S_{10}}\epsilon + \left(\frac{S_{12}}{S_{10}} - \frac{S_{11}^2}{2S_{10}^2}\right)\epsilon^2 + \dots \\ \log\frac{S_{20}}{S_2(0)} + \frac{S_{21}}{S_{20}}\epsilon + \left(\frac{S_{22}}{S_{20}} - \frac{S_{21}^2}{2S_{20}^2}\right)\epsilon^2 + \dots \\ \log\frac{S_{30}}{S_3(0)} + \frac{S_{31}}{S_{30}}\epsilon + \left(\frac{S_{32}}{S_{30}} - \frac{S_{31}^2}{2S_{30}^2}\right)\epsilon^2 + \dots \\ \log\frac{S_{40}}{S_4(0)} + \frac{S_{41}}{S_{40}}\epsilon + \left(\frac{S_{42}}{S_{40}} - \frac{S_{41}^2}{2S_{40}^2}\right)\epsilon^2 + \dots \end{pmatrix} =$$

$$\tilde{A} \begin{pmatrix} a_1 & \epsilon\sqrt{a_1a_2} & \epsilon\sqrt{a_1a_3} & \epsilon\sqrt{a_1a_4} \\ \epsilon\sqrt{a_1a_2} & a_2 & \epsilon\sqrt{a_2a_3} & \epsilon\sqrt{a_2a_4} \\ \epsilon\sqrt{a_1a_3} & \epsilon\sqrt{a_2a_3} & a_3 & \epsilon\sqrt{a_3a_4} \\ \epsilon\sqrt{a_1a_4} & \epsilon\sqrt{a_2a_4} & \epsilon\sqrt{a_3a_4} & a_4 \end{pmatrix} \begin{pmatrix} S_{10} + \epsilon S_{11} + \epsilon^2 S_{12} + \dots - S_1(0) \\ S_{20} + \epsilon S_{21} + \epsilon^2 S_{22} + \dots - S_2(0) \\ S_{30} + \epsilon S_{31} + \epsilon^2 S_{32} + \dots - S_3(0) \\ S_{40} + \epsilon S_{41} + \epsilon^2 S_{42} + \dots - S_4(0) \end{pmatrix} \tag{3.10}$$

Equating the coefficients of ϵ^0 we use MATLAB to solve the non-linear equations to find the S_{j0} terms:

$$\log\frac{S_{j0}}{S_j(0)} = \tilde{A}a_j(S_{j0} - S_j(0)) \tag{3.11}$$

There are two solutions to this equation: the trivial case where $S_{j0} = S_j(0)$ and where $S_{j0} < S_j(0)$. We are interested in finding the second solution where the infection is present in the population, but if $R_0 < 1$ we know that there is no epidemic so we do not need to solve this system.

By equating higher powers of ϵ we calculate the terms S_{j1} to S_{j4} , where $j \in \{1, 2, 3, 4\}$, so we gain the number of susceptibles remaining in each age category at the end of each epidemic. We do not expand past ϵ^4 as the terms become negligible.

From this solution of the asymptotic expansion, we gain the number of people who are infected in one epidemic. We now wish to iterate this process and allow for population changes at the end of each year. An amended reproduction ratio, R_n, is calculated each year to take account of the change in the susceptible population. It is no longer the basic reproduction ratio as the entire population is no longer susceptible to infection, but is still a measure of spread of the infection in the population each year.

$$R_n = \rho\left(M^{(n)}\right) \tag{3.12}$$

where $M^{(n)}$ is the next generation matrix calculated using the number of susceptibles for each age group at year n.

At the end of each year we let a proportion of the remaining susceptible population from each age class move into the next age class and introduce new susceptibles into the population, to account for demographic change. Each epidemic of measles is completed within a year, so we have the two time scales to work on, with the integral equation for the epidemic numbers being solved without having to account for demographic change while it is happening. As the first age group does not encompass an entire year (6 months to 15 months old), we have new susceptibles introduced into both the first and second age

groups.

$$
\begin{aligned}
S_l^{(n+1)}(0) &= B\frac{15-6}{12} \\
S_2^{(n+1)}(0) &= S_1^{(n)}(\infty) + \left(1 - \frac{15-6}{12}\right) B + \left(1 - \frac{1}{5-\frac{15}{12}}\right) S_2^{(n)}(\infty) \\
S_3^{(n+1)}(0) &= \frac{1}{5-\frac{15}{12}} S_2^{(n)}(\infty) + \left(1 - \frac{1}{11-5}\right) S_3^{(n)}(\infty) \\
S_3^{(n+1)}(0) &= \frac{1}{11-5} S_3^{(n)}(\infty) + \left(1 - \frac{1}{25-11}\right) S_4^{(n)}(\infty)
\end{aligned} \tag{3.13}
$$

where $S_j^{(n)}(\infty)$ is the final size of the susceptible population at the end of year n. We then calculate the reproduction ratio for that year using Equation (3.12). By repeating this process, we derive a model for the epidemic pattern over many years, with the predicted number of people infected each year and the reproduction ratio. From the way in which we do the demographic adjustment at the end of each year, it is assumed that once infected a person cannot become infected again – even after recovering form the virus.

A summary of the parameter values we use in this model and a brief description are given in Table 3.1.

Parameter Name	Value	Meaning
ϵ	0.4	Weighting to inter-class mixing
a_1	1	Activity level for 6–15 months old
a_2	3	Activity level for 15month – 5 years old
a_3	6	Activity level for 5–11 years old
a_4	3	Activity level for 11–25 years old
B	57435	Birth rate
$S_1(0)$	$B\left(\frac{15-6}{12}\right)$	Initial population for 6–15 months old
$S_2(0)$	$B\left(5-\frac{15}{12}\right)$	Initial population for 15 month –5 years olds
$S_3(0)$	$B(11-5)$	Initial population for 5–11 years old
$S_4(0)$	$B(25-11$	Initial population for 11–25 years old

Table 3.1: Parameter values and descriptions for the integral equation model for repeated measles epidemics.

3.3 Model results

Using MATLAB to complete the asymptotic expansion to give the number of susceptibles remaining in each age group after an epidemic and then complete the inter-class movement at the end of each year, we plot the susceptible population in each age group at the end of each year (before the change over of susceptibles between age groups and the introduction

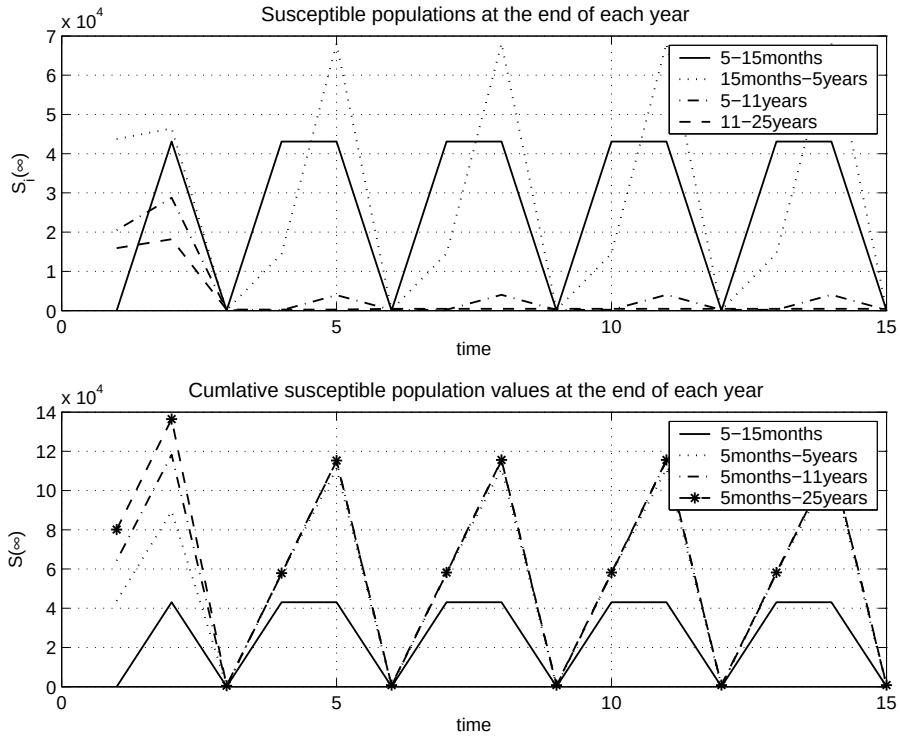


Figure 3.1: For this example, $R_0 = 12.8$. Top: The number of susceptibles in each age group at the end of the year, i.e. before people are moved between groups and new susceptibles introduced into the population. Bottom: Cumulative susceptible populations at the end of each year. The lowest line is the first age group, the next plotted line represents the sum of age groups 1 and 2, the third line represents the total susceptible population in groups 1-3 inclusive, and the highest line is the total susceptible population (5 month – 25 year olds) at the end of each year.

of new susceptibles) in Figure 3.1 (top figure). The cumulative susceptible population at the end of each year is shown in Figure 3.1 (bottom figure), where the lowest curve is age group one susceptible, the second curve is age groups one and two susceptible, to the top curve which represents the total number of susceptibles each year. It can be clearly seen in Figure 3.1 that the susceptible population reaches a peak every three years before it reduces, so our population is experiencing epidemics of measles every three years. The largest susceptible populations are in our bottom two age groups, which are the two age classes that have newborns included into at the end of each year. The older age groups do not have a large susceptible population, as by the time children reach these classes, the majority of them have already been infected.

The asymptotic expansion was only used to solve our model if the reproduction ratio came out to be greater than one. If the reproduction ratio was less than one, an epidemic was assumed not to occur, so the number of susceptibles in the population for the year remaining unchanged and only demographic changes were allowed. Figure 3.2 shows the

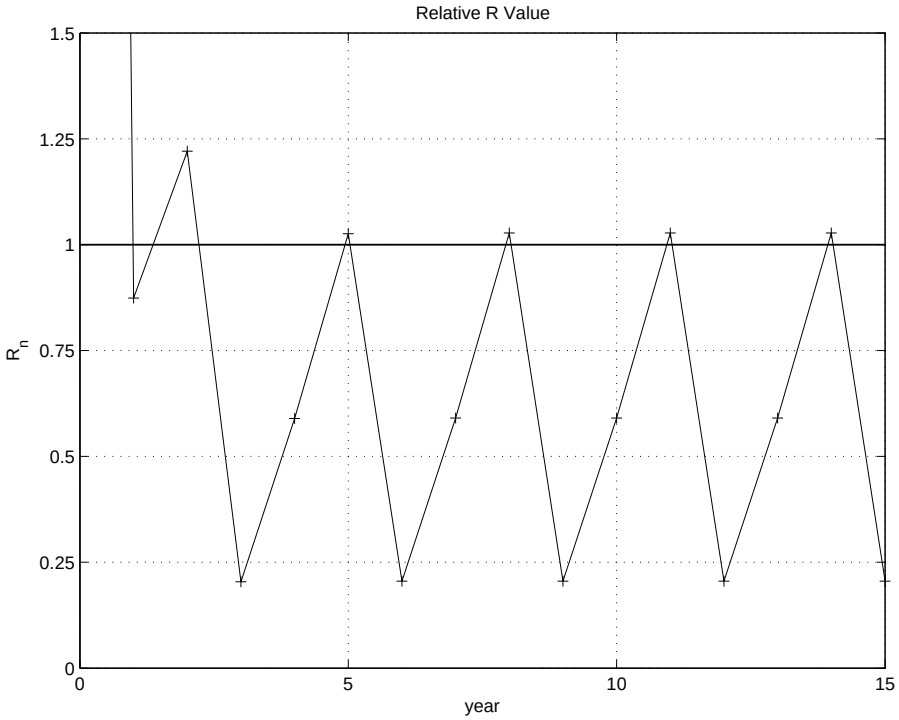
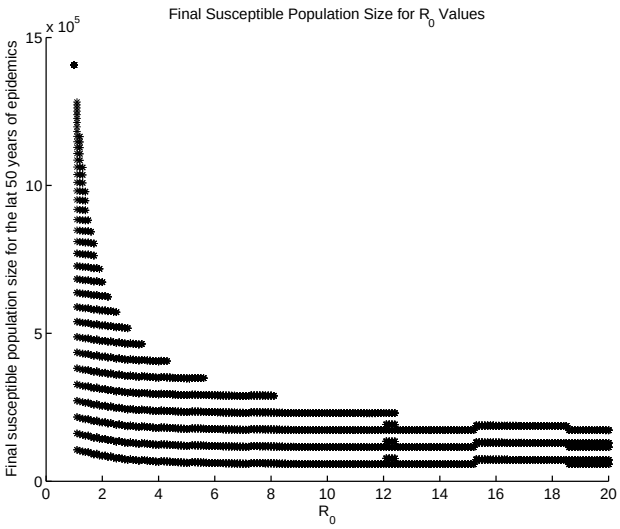


Figure 3.2: The relative reproduction ratio values calculated at the end of each year for the entire population, with initially $R_0 = 12.8$.

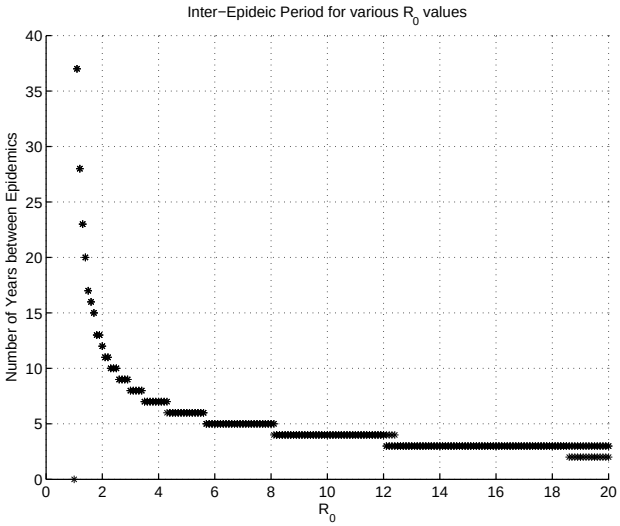
effective reproduction ratio as the disease progresses through the population. We can see that the basic reproduction ratio is only just increasing over one every third year, which means an epidemic occurs and the asymptotic expansion has to be solved.

By varying the basic reproduction ratio and running the model for fifty years for the epidemic pattern to establish, we gain Figure 3.3(a), showing the final susceptible population size. In Figure 3.3(b) we can see the number of years between epidemics for varying values of R_0. As R_0 increases the inter-epidemic period generally decreases, however we see that for some values of R_0 we have two different inter-epidemic periods. For example when $12 \leq R_0 \leq 12.6$ epidemics occur after 4 years, then after 3 years alternately as demonstrated in Figure 3.4(a) and a similar pattern also occurs when $R_0 > 18.6$, as shown in Figure 3.4(b) where $R_0 = 18.6$ and we see epidemics occur on an alternating 2 year to 1 year time scale.

To vary the value of R_0 in our model we are actually varying the value of $\tilde{A}$ (the probability of being infected given contact with an infectious person). All other values in model remain unchanged for these calculations.

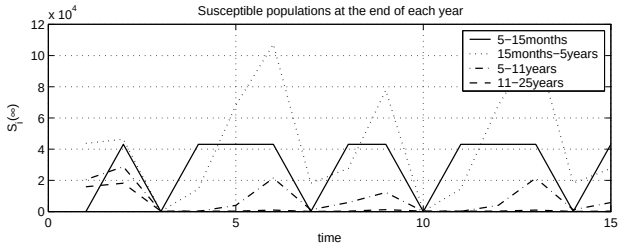


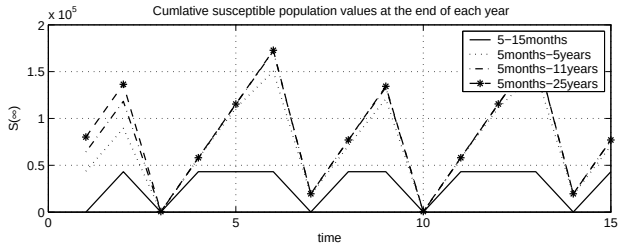
(a)



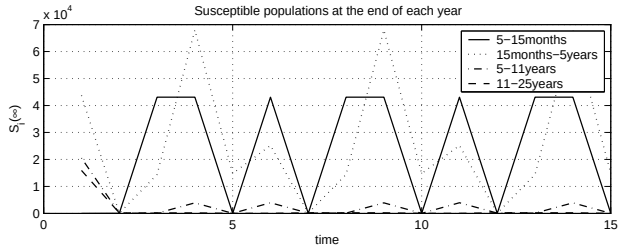
(b)

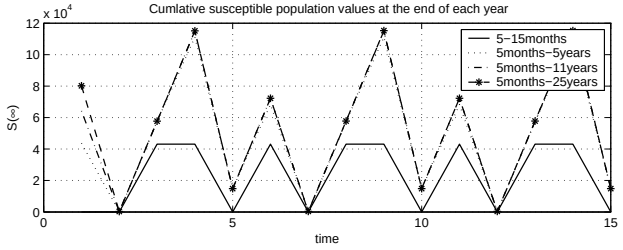
Figure 3.3: Using different values for R_0, in Figure (a) the model is run for 200 years, then the next 50 years final susceptible population is plotted. As R_0 increases, the number of susceptible populations for each value decreases, showing that the epidemic pattern begins to settle. For Figure (b), the model is run for 200 years, then the final 50 years of data is used to calculate the number of years between epidemics.





(a)





(b)

Figure 3.4: (a) is when $R_0 = 12.4$. (b) When $R_0 = 18.6$. For both figures, the top figure is the number of susceptibles in each age group at the end of the year and the bottom figure is the cumulative susceptible populations at the end of each year.

3.4 Discussion

Without vaccination present in the population, measles epidemics in New Zealand were observed every two years, yet our model shows repeated epidemics every three years when a basic reproduction ratio of 12.8 is used. The largest epidemics are seen in the 15 month to 5 year age group, with the smallest epidemics in the 15–25 year age group. As the first age group width is less than a year, the discrete mapping from year to year does not quite make sense, and also explains why there is never an epidemic within that age group (this is something that could be changed in the future). The basic reproduction ratio reduces substantially after the initial epidemic, and never increases back to that level ($R_0 = 12.8$) – if it increases above one an epidemic occurs. To modify our model to gain the two yearly epidemic pattern, the probability of being infected given contact with an infective (the vector $A(\tau)$) could be increased, thus increasing R_0 to be much higher than the predicted value given by Roberts & Tobias (2000).

To find the number of people infected during the course of an epidemic, the final size equation was solved. It is always assumed that an epidemic will be over within a year (as is historically the case with measles epidemics in New Zealand). Theoretically, it is possible for an epidemic to span over a number of years, in which case the discrete mapping would need to be changed in our model to allow for a greater number of people to move between age groups once the epidemic is over.

The differential equations model Roberts & Tobias (2000) successfully modelled the two yearly epidemic pattern when no vaccination was present in the population. If a population is not structured (i.e. the one dimensional case) both the integral equation model and the differential equation model (SIR model) produce the same results, yet it has been demonstrated here that with a structured population the models differ substantially in their results.

A similar integral equation method has been used by Andreasen & Frommelt (2005) using single year age groups, and has shown analytically that when the transmissibility of infection is different for each age class, three year limit cycles appear. Both our model and Andreasen & Frommelt (2005) do not include a seasonal forcing, as the population demographics are calculated separately from the epidemic process, yet it is known that seasonal forcing is required to make a differential equation model exhibit the repeated epidemic pattern. Andreasen & Frommelt (2005) looked at the dynamics of of the yearly epidemics in terms of parameter values, concentrating on the stability of steady states, rather than comparing the model results with known data.

Numerical problems were encountered when solving the nonlinear Equation (3.11), as to find the non-trivial solution we need $\tilde{A}a_j > 1$ which is not always true when $R_0 > 1$ (as R_0 is calculated form the entire system rather than solely relying on the diagonal entries in the next generation matrix). To work around this problem, in the instances when $\tilde{A}a_l < 1$ for any of the age groups, the system was solved for the entire population, and then the solution was distributed accordingly amongst the age groups. After running

several simulations it was found that this was always the case – that is, the years where there are epidemics either one or all $\tilde{A}a_l < 1$.

Ma & Earn (2006) shows that the final size equation has a unique non-trivial solution, when the contact matrix is a positive, stochastic matrix, with largest eigenvalue one, and the probability of being infected given contact is constant and the same for every age group. If the contact matrix does not satisfy these conditions, or the probability of infection given contact is different for each age group, then the final size equation cannot be used. Ma & Earn (2006) show the existence and uniqueness of solutions to the final size equation when used for age structured and spatially structured population, but they do not actually find the solutions.

Chapter 4

Review and Extensions to the Medley *et al.* (2001) Hepatitis B Virus Model

4.1 Introduction

Hepatitis was first identified as being transmitted through blood in Germany in 1883, but it was not until 1947 that the term Hepatitis B virus (HBV) was proposed. The surface antigen for the virus, HBsAg, was identified in 1967, and is now used for the vaccine against HBV (New Zealand Ministry of Health, 2002). Hepatitis B has the second highest death rate for vaccine preventable diseases in New Zealand (New Zealand Ministry of Health, 2002) and is the leading cause of liver cancer in the world (The Hepatitis Foundation of New Zealand, 2007).

Hepatitis means inflammation of the liver cells (Macpherson, 1992), which may be acute or chronic. There are five viruses that cause hepatitis, called hepatitis A, B, C, D and E. Hepatitis A and E viruses cause infectious hepatitis, transmitted by eating food contaminated with faecal material from an infected individual. Viruses B, C and D are called serum hepatitis and are transmitted by contact with blood or body fluids of an infected person. Hepatitis B virus, the most serious type of viral hepatitis (World Health Organisation, 2000), can cause acute infection, chronic carrier status and chronic hepatitis. Hepatitis B virus is the only hepatitis virus causing chronic hepatitis that is vaccine preventable.

HBV is transmitted through infected blood or bodily fluids in the same way as human immunodeficiency virus (HIV) — although HBV is 50–100 times more infectious than HIV (World Health Organisation, 2000). The most common ways of being infected are: from mother to baby at birth; child-to-child transmission; through intravenous drug use, and unprotected sexual activity.

Once infected with HBV there is an incubation period of four to ten weeks, the surface

antigen HBsAg then becomes detectable in the blood, with anti-HBc antibodies detectable shortly after (Ganem & Prince, 2004). Another surface antigen, HBeAg, is then released into the blood indicating that the virus is infecting the liver cells and that the host is highly infectious. If the infection is going to clear, the levels of antigen HBsAG and HBeAg recede from circulation and the anti-HBs antibodies become detectable — this is when a patient is classed as immune from further HBV infection. During this period symptoms of infection may last for several weeks and can include jaundice (yellowing of the skin), fatigue, nausea, vomiting and abdominal pain (World Health Organisation, 2000). However, about 60% of infected individuals will be asymptomatic (New Zealand Ministry of Health, 2002). Following this acute phase of the disease there is a long period of recuperation lasting several months to a year. Acute hepatitis occurs only rarely in infants, in about 6% of infected children and in 33% of infected adults, and will scarcely (2%) be fatal in all age groups (New Zealand Ministry of Health, 2002).

If the infection does not produce an effective immune response a chronic carrier (CHB) state may develop, where the virus survives and continues to replicate in the body for many years. In this state the antigen HBsAg remains detectable in the blood six months after the initial infection (Juszczyk, 2000). The chance of becoming a chronic carrier depends on the age at initial infection: 90% of newborns (up to six months old), 25–50% of children aged under 5 years old and 5–10% of adults who are infected develop CHB (Juszczyk, 2000; New Zealand Ministry of Health, 2002; World Health Organisation, 2000). People with CHB will often have no history of acute illness. Patients with CHB may develop cirrhosis (liver scarring) that can lead to liver failure, and they may also develop liver cancer (The Hepatitis Foundation of New Zealand, 2007). A small portion (1–6%) of chronic carries will clear the virus naturally (New Zealand Ministry of Health, 2002; The Hepatitis Foundation of New Zealand, 2007).

4.2 Literature Review.

There have been numerous mathematical models published on hepatitis B, but none specifically targeted at the New Zealand situation, where we have overall low endemic rates of disease, with medium to high rates in certain regions of the country. In this section we shall highlight some of the models relevant to our current study.

Similar to meningococcal disease, a key feature of Hepatitis B disease is the carrier state, where an individual is asymptomatic but still infectious. Edmunds *et al.* (1993) examined the relationship between age at infection with HBV and the development of the carrier state. They fitted an exponential model to the data collected from over 30 sources/published results and found that the proportion of people who become carriers decreases with the age at infection. Their maximum likelihood solution for the model is used in a later model (Medley *et al.*, 2001), and we will use a simplified version of it in our model, as will be discussed in detail in section 4.3.

Williams *et al.* (1996) used an age and sexual orientation dependent partial differential equation model with six compartments: susceptible to infection, latently infected, acutely infected, immune following infection, chronic carrier and immune following vaccination. Each of these compartments is split into 12 age classes, with the rate of acquiring sexual partners varying for each age group. They have assumed that there is no risk of infection after birth until the onset of sexual activity, and that there are births into three compartments: susceptible, vaccinated immune and latent (as a results of vertical transmission). This assumption of no infection for children under the age of 15 does not allow for child-to-child infection, and there is also no infection after the age of 60 as sexual activity is assumed to be zero. They assumed the duration of carriage to be 65 years, and there to be an extra mortality rate due to acute and chronic infection. The risk of becoming a carrier following acute infection is kept constant for all age groups at 10%. Their results for the endemic steady state are consistent with the data from the United Kingdom for the proportion of people who are seropositive for HBV (have been infected at some stage in their lives), with an estimated basic reproduction ratio of 1.2 for the heterosexual population and 4 for the homosexual population. The difference in the value R_0 for the two sub populations can be attributed to the different rates of change of partners and different tranmission risks for each population (the homosexual population has a higher risk of transmission). Williams *et al.* predict that targeted vaccination at genito-urinary clinics would have a more rapid response then mass infant or adolescent vaccination, as there is no lag in the effect (measured by decrease in carrier prevalence), and it is highly targeted.

Kretzschma *et al.* (2002) look at the effect of vaccination against HBV in countries with low endemic status, using (Williams *et al.*, 1996) as a basis for their model. They add in the effect of immigration of Hepatitis B virus carriers from countries with higher disease prevalence, and compare their results to data from the Netherlands. They also make a key change to the Williams *et al.* (1996) model by allowing the probability of becoming a carrier depend on age at infection. The population remains at a constant size, with rescaling taking place to allow for a constant annual net per capita rate of immigration, with a fixed age distribution and constant prevalence of carriers and immunes. These key changes lower the basic reproduction ratio for the heterosexual population to 0.53 and the homosexual population to 2.66. In the heterosexual population, the disease endemicity is maintained by the constant influx of carriers immigrating. They consider three levels of immigration relative to their carrier levels, and find the effect of universal vaccination of newborns to have little effect on the prevalence of carriers in all cases, as the force of infection will not decrease substantially with vaccination. They predict that vaccination would need to be maintained for decades in order to protect the population.

Anderson & May (1992) give a simple SEICR model, where the carrier state is presumed to be lifelong, and the average age at infection is 5–7 years old. Their model gives a basic reproduction ratio of six, with non-carriers being ten times more infectious

than carriers. The presence of carriers in the population is the source of the infection, so the disease cannot be totally removed from the population unless the vaccination affects carriers. If the vaccination does not affect carriers (which is the case of the vaccine used in New Zealand), the disease will not be eliminated until the carriers have all died. They also state that as the carriers are a source of infection, they eliminate the oscillations or repeated epidemic peaks that are seen with diseases that do not have the carrier state.

The simple model by Anderson & May (1992) is expanded by Wilson *et al.* (1998) to consider a variant of the infection that escapes vaccination in a highly endemic area. They present a seven compartment model: susceptibles; vaccinated; infected with primary HBV infection; infected with a variant; chronic carriers of either type of infection and recovered. Their model is not structured by age, so infection is transmitted horizontally through age-independent mixing and vertically through chronic carrier mothers. They assume that carriers are only 16% as infectious as acutely infected individuals, and (as there is no age structure) let 30% of those infected go on to become carriers. Under the worst case scenario that vaccination provides no protection against the variant strain, it takes decades for the variant strain to emerge in the population. This model is not really concerned about the current levels of hepatitis B disease, but the possibility that a vaccine resistant strain could emerge, and hence their results are not directly compared to any known data.

The model presented by McLean & Blumberg (1994) concentrates on areas with a high carrier prevalence, where the whole population is at a high risk of infection. They split the population into six compartments with relation to the infection process: susceptible; primary infected; immune; infectious carrier; non-infectious carrier and vaccinated. They consider three possible causes of disease transmission: perinatal and vertical transmission from infectious mothers to their children; casual (non-sexual) transmission among the whole population; and sexual transmission amongst individuals in the the sexually active classes. McLean & Blumberg allow two different proportions of children to be born into the infectious class depending on the status of their mothers – whether they are infectious or non-infectious carriers at the time. The probability of carriage after infection depends on their age and sex at the time of infection (decreasing with age and higher in males), and force of infection depends on the size of the infectious population. There are two different forces of infection – for casual transmission and sexual transmission for male and females, with the force for sexual transmission relating to partner change rates. An additional death rate is included for both carrier compartments, and this is dependant on age and sex. The effect of the vaccination is assumed to wane over the years, with the average protection period of 22.2 years, whereas immunity after being infected is assumed to be lifelong. The model's results are not compared with any data, and no model results are actually presented – only the formulation of parameter estimates based on data from the United Kingdom. This model is a framework that could be used to predict the outcomes of various vaccination schemes on the number of acute infections and carriers present in the population.

A SEICR type model is presented by Zhao *et al.* (2000), with the population split into susceptibles, latently infected, temporary carrier, chronic carrier and immune. Both the carrier compartments are infectious, with the force of infection dependent on age and the time after vaccination is introduced. The force of infection peaks in infancy and early childhood, and declines rapidly with age, being low from 15 years old onwards – they have used a cubic function in age. They assume that immunity after infection or through vaccination is lifelong, and there is an additional death rate for those in the chronic carrier state dependant on age. The probability of becoming a chronic carrier is also dependant on age, using an exponential expression similar to that given by Edmunds *et al.* (1993). The rate at which chronic carriers become immune is also dependant on age, with the rate for over 50 years old being much higher than before 30, a low reversion rate in people between 5–45 years old, and no reversion for those under 5 years old. This could be explained by the decrease in carriers over the age of 50 in the data they have based their model on, meaning there is a higher death rate for carriers than for non-carriers. The model fits well to the prevalence and carriage of HBV by age, before and after vaccination is included in their model. They predict that carriage rates will remain high even after vaccination, and the only drop in carriage rates will be when the existing carriers die. They assumed that with a 100% vaccination coverage and 90% effectiveness of the vaccine, it would take nearly 70 years to eliminate the acute infection in the population, as the incidence ratio of carriers takes nearly 25 years to start to decline after the introduction of the vaccination.

A very simple susceptible, infectious, carrier model is presented by Edmunds *et al.* (1996) for areas that are highly endemic (more than 75% of the adult population has evidence of past or current infection). They assume that the probability of developing carriage is a non-linear decreasing function of age, and that the force of infection is also dependent on age (they used two different methods for calculating the force of infection – one dependent on the number of susceptibles in the neighbouring age classes, and the other a continuous polynomial of order 1–4). Key characteristics of high endemic areas are a low average age at infection and a high prevalence of carriers. Comparing their model to data from high prevalence areas, they found the force of infection to be highest in young children and to decline throughout childhood – which corresponds to the probability of becoming a carrier depending on age at infection. Both of the high prevalence areas that their data were taken from showed that horizontal transmission was highest in children, but East Asia had a slightly higher prevalence of vertical transmission than sub-Saharan Africa. They predicted that a mass infant vaccination campaign would decrease the generation of carriers, and it is this age group that is most likely to become carriers after infection.

Goldstein *et al.* (2005) present a model to estimate the morbidity and mortality from hepatitis B virus and the impact of vaccination on the morbidity and mortality, and also the development of the acute form of the infection and the carrier stage. Their model can be run through a simulator on the Center for Disease Controls website (Center for Disease Control, 2008). Few details of the actual model are given in the paper and their model

requires population–specific data in order to run: the number of new borns surviving past the first year of life; the prevalence of infectious and carrier women of child bearing age and the prevalence of acute and carrier infection among five year olds and the above 30 years old. If the effect of vaccination is to be included in the model outputs, the proportion of the surviving newborn age class that is expected to receive the vaccine and the proportion expected to receive the full course of the vaccine are also required. Given these inputs (that would be hard to estimate for many countries due to the carrier population being largely unknown), the model will calculate the disease burden for a specific year and for a specific new born age group over the course of their lifetime. They have included an age specific risk of infection and probability of acute and chronic infection, but no details are given as to how the model works. Goldstein *et al.* give estimates for the current (year 2000) and future burden of infection in various parts of the world but do not directly compare these to any known data. Their model is intended to be used as a tool for countries to see the impact of infant vaccination campaigns.

We now go on to look in detail at Medley *et al.* (2001), as this model stood out from all other papers as it shows a possibility for the infection to be endemic in the population even when the basic reproduction number is less than one.

4.3 Critical Review of Medley *et al.* (2001).

We will use the paper (Medley *et al.*, 2001) as the basis for our work, as their model exhibits interesting dynamics while still modelling many of the critical aspects of HBV.

Medley *et al.* (2001) present a susceptible, exposed, infectious, carrier and removed (SEICR) differential equation model, with a constant population size. As the force of infection is inversely related to the age at infection, they have assumed that the probability of becoming a carrier will depend on the force of infection. Letting x be the proportion of the population susceptible to infection; h be the proportion who are infected but not yet infectious; y be the proportion who are acutely infected; c be the proportion who are carriers; and r be the proportion who are immune, the differential equations for the model are:

$$\begin{aligned}
\frac{dx}{dt} &= -(\lambda+\mu)x + \mu\omega(1-\nu c) \\
\frac{dh}{dt} &= \lambda x - (\sigma+\mu)h \\
\frac{dy}{dt} &= \sigma h - (\gamma_1+\mu)y \\
\frac{dc}{dt} &= q(\lambda)\gamma_1 y - (\gamma_2+\mu)c + \mu\omega\nu c \\
\frac{dr}{dt} &= [1-q(\lambda)]\gamma_1 y + \gamma_2 c - \mu z + \mu(1-\omega)
\end{aligned} \tag{4.1}$$

The parameters and their values are described in Table 4.1. The force of infection, λ, depends on the proportions of acutely infected and carriers in the populations: $\lambda =$

$\beta(y + \alpha c)$.

Medley *at al.* have used the result that the average age at infection is inversely related to the force of infection, and so have let $\lambda = 1/p$ in the function for carriage development given by Edmunds *et al.* (1993):

$$q(\lambda) = f + (1 - f)\exp(-0.645\lambda^{-0.455}) \tag{4.2}$$

We see that $q(\lambda)$ is an increasing function in λ, with the lowest value it can take being f. The authors state that this will essentially be the probability of an adult developing carriage.

Symbol	**Parameter Description**	**Value**
σ	the rate at which latently infected individuals become infective	6 per year
γ_1	the rate at which acutely infected individuals recover	4 per year
γ_2	the rate at which carrier individuals recover	0.025 per year
ν	the proportion of unimmunised children born to carrier mothers who develop carriage	0.11
$1 - \omega$	the proportion of infants who are successfully immunised	refer to text
β	transmission coefficient	refer to text
α	infectiousness of carriers relative to acutely infected individuals	$0 \leq \alpha \leq 1$
μ	birth/death rate	1/70 per person per year

Table 4.1: The parameters and variables used in the model given by Medley *et al.* (2001)

For numerical computation, we calculated the steady states of the model by substituting $x = 1 - (h + y + c + z)$ and solved as a system with respect to λ:

$$\begin{pmatrix} \sigma + \lambda + \mu & \lambda & \lambda & \lambda \\ \sigma & -(\gamma_1 + \mu) & 0 & 0 \\ 0 & q(\lambda)\gamma_1 & \nu\mu - (\gamma_2 + \mu) & 0 \\ 0 & (1 - q(\lambda))\gamma_1 & \gamma_2 & -\mu \end{pmatrix} \begin{pmatrix} h \\ y \\ c \\ z \end{pmatrix} = \begin{pmatrix} \lambda \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

To solve this, we fix the value of λ and solve to find the values of h, y, c and z. Once these are know, it is simple to calculate x.

We can calculate the basic reproduction ratio for this model by first considering the next generation matrix, K. We note that there are two host types in this model: those

who are infected through contact with an acutely infected or carrier individual; and those who are infected at birth. The components of the next generation matrix are given by:

$K_{1,1}$: Acutely infected individuals infect others at rate β, and remain infectious for $\frac{1}{\gamma_1+\mu}$ years. A proportion, $q\gamma_1$, of acutely infected individuals become carriers and infect others at rate $\alpha\beta$, and remain infectious for $\frac{1}{\gamma_2+\mu}$ years. Of those who are infected, a proportion $\frac{\sigma}{\sigma+\mu}$ become infectious.

$K_{1,2}$: Carriers infect others at rate $\alpha\beta$, and remain infectious for $\frac{1}{\gamma_1+\mu}$ years. A proportion, $\frac{\sigma}{\sigma+\mu}$, of those infected go on to be infectious.

$K_{2,1}$: A proportion, $q\gamma_1$, of acutely infected individuals go on to become carriers, who then remain carriers for $\frac{1}{\gamma_2+\mu}$ years. Carriers give birth at rate μ, and a proportion, ν, of these births are carriers.

$K_{2,2}$: Carriers give birth at rate μ, then a proportion of these, ν, go on to become carriers. Carriers remain in that compartment for $\frac{1}{\gamma_2+\mu}$ years.

Thus, the next generation matrix for the Medley *et al.* (2001) model is:

$$K = \begin{pmatrix} \frac{\sigma}{\sigma+\mu}\frac{\beta}{\gamma_1+\mu}\left(1+\frac{q(0)\gamma_1\alpha}{\gamma_2+\mu}\right) & \frac{\sigma}{\sigma+\mu}\frac{\alpha\beta}{\gamma_2+\mu} \\ \frac{q(0)\gamma_1\nu\mu}{(\gamma_1+\mu)(\gamma_2+\mu)} & \frac{\mu\nu}{\gamma_2+\mu} \end{pmatrix}$$

The basic reproduction ratio is then given by the largest eigenvalue of the next generation matrix, i.e. the largest root of the quadratic:

$$R^2 - R\left(\frac{\sigma\beta(\gamma_2+\mu+q(0)\gamma_1\alpha)+\nu\mu(\sigma+\mu)(\gamma_1+\mu)}{(\sigma+\mu)(\gamma_1+\mu)(\gamma_2+\mu)}\right) + \frac{\nu\mu\sigma\beta}{(\sigma+\mu)(\gamma_1+\mu)(\gamma_2+\mu)} = 0 \tag{4.3}$$

This is different to the R_0 given in Medley *et al.* (2001) (for which no justification was given), however it leads to similar analytic results.

Solving Equation (4.3) numerically and plotting the proportion of the population who are seropositive to the infection ($1-x^*$) against the basic reproduction ratio we obtain Figure 4.1 - which is similar to the results given by Medley *et al.* even though we have used a different formula for R_0. By varying the value of the parameter f (that is seen as the probability of adults developing carriage), we see that we can have the situation where the infection persists in the population even when the basic reproduction ratio is below one. The dashed parts of the curves represent an unstable steady state, and the solid parts of the curves represent a stable steady state. If the value of f is low enough, we can have a hysteresis effect – for example consider the $f=0$ curve in Figure 4.1: if the proportion of the population that is seropositive to the infection is 0.2 and R_0 is increased, the proportion of the population that is seropositive will "jump" to the upper branch of the curve close to 1. Once this has occurred, if R_0 is lowered, $1-x^*$ will decrease until

it reaches the unstable steady state and it "jumps" from there to the $1 - x^* = 0$ steady state. If the function $q(\lambda)$ is constant, the backwards bifurcations do not occur, and the graph behaves as the right most curve in Figure 4.1.

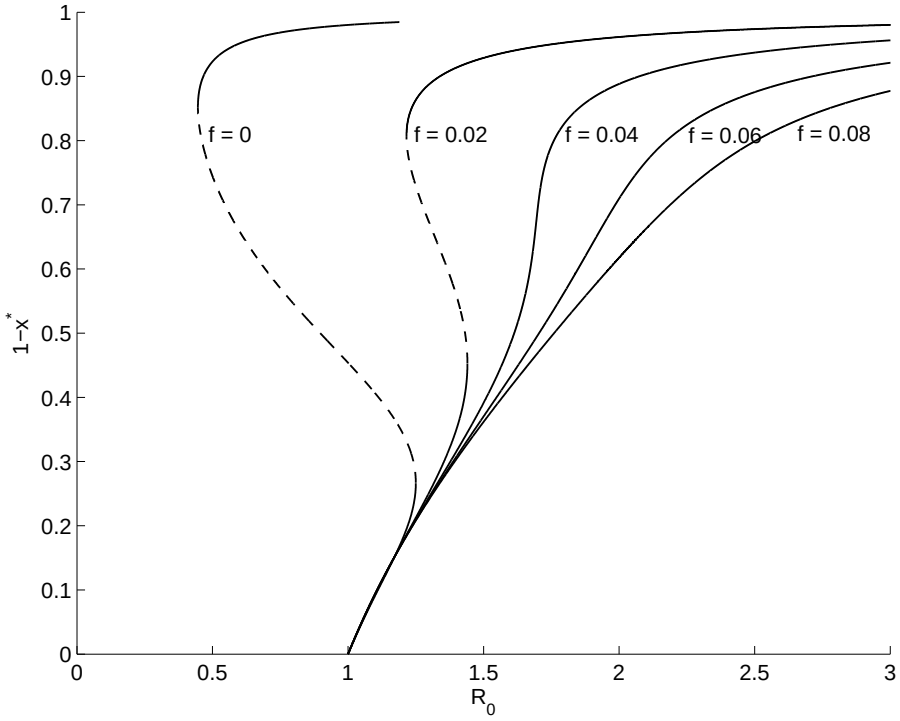


Figure 4.1: The steady state proportion of the seropositive population plotted against R_0 for varying values of f. As f increases, we see that the backwards bifurcation vanishes. For all the curves, $\alpha = 1$. The dashed lines are unstable steady states, and the solid lines are stable steady states. The line $1 - x^* = 0$ is a stable steady state when $R_0 < 1$ and unstable afterwards.

Figure 4.2 shows the combinations of the parameters f and α that produce a backwards bifurcation in the R_0 versus proportion seropositive graph. This was found by numerically calculating the steady state values for varying values of λ, for each combination of α and f, and plotting the point where R_0 decreases from the previous iteration. This leads to an interesting question: what conditions need to be met for the backwards bifurcation to occur, and more specifically, what part of the definition of the function $q(\lambda)$ causes the backwards bifurcation? To explore this further, we analytically find the steady states of Equation (4.1).

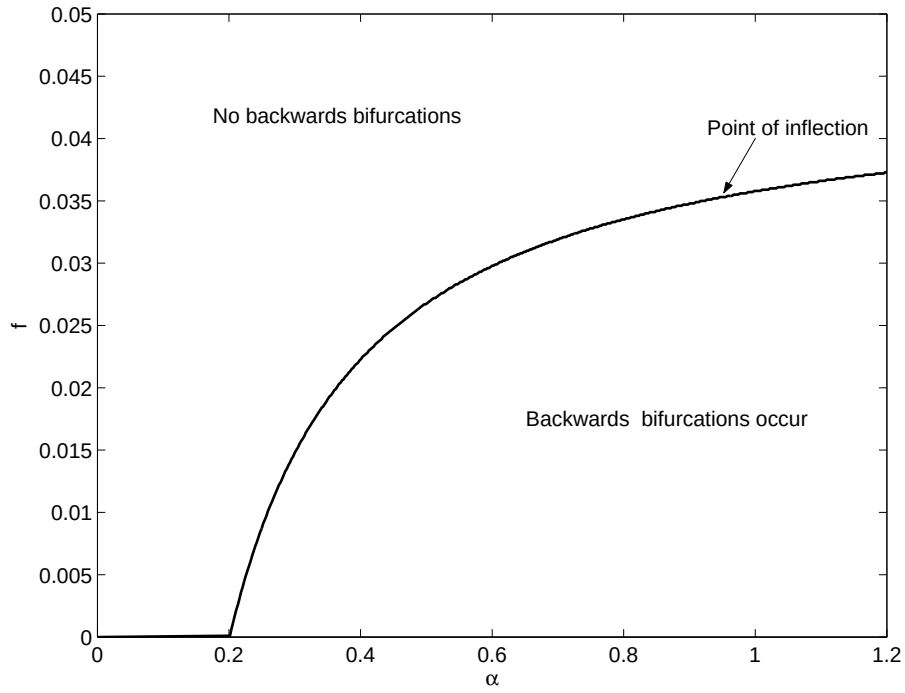


Figure 4.2: The values of the two parameters α and f that produce a backwards bifurcation in the R_0 versus proportion seropositive curve.

The steady state for the system of Equations (4.1):

$$\frac{dh}{dt} = 0 \Rightarrow \qquad h^* = \frac{\beta(y^* + \alpha c^*)x^*}{\sigma + \mu} \tag{4.4}$$

$$\frac{dy}{dt} = 0 \Rightarrow \qquad y^* = \frac{\beta\sigma\alpha c^* x^*}{A - \beta\sigma x^*} \tag{4.5}$$

$$\frac{dc}{dt} = 0 \Rightarrow \qquad x^* = \frac{AD}{\sigma\beta(q(\lambda^*)\gamma_1\alpha + D)} \tag{4.6}$$

$$\frac{dx}{dt} = 0 \Rightarrow \qquad c^* = \frac{\mu(x^* - \omega)(A - \beta\sigma x^*)}{\beta x^*(\sigma\mu\omega\nu - \alpha A) - \mu\omega\nu A} \tag{4.7}$$

$$c^* = \frac{q(\lambda^*)\gamma_1\mu(\omega\sigma\beta(q(\lambda^*)\gamma_1\alpha + D) - AD)}{\beta(AD + \mu\omega\nu\sigma q(\lambda^*)\gamma_1)(q(\lambda^*)\gamma_1\alpha + D)} \tag{4.8}$$

where $A = (\gamma_1 + \mu)(\sigma + \mu)$ and $D = \gamma_2 + \mu - \mu\nu\omega$. We also know:

$$\begin{aligned} \lambda^* &= \beta(y^* + \alpha c^*) \\ &= \frac{\mu(\omega\sigma\beta(q(\lambda^*)\gamma_1\alpha + D) - AD)}{AD + \mu\omega\nu\sigma q(\lambda^*)\gamma_1} \end{aligned} \tag{4.9}$$

We want to find what conditions lead to $\frac{dR_0}{dx^*} = 0$, giving us the backwards bifurcation in Figure 4.1. As R_0 is the largest eigenvalue of the next generation matrix, K, from Equation (4.3) we know R_0 will be the largest root of:

$$R^2 - R\left(\frac{\sigma\beta}{A}\left(1 + \frac{f\gamma_1\alpha}{\gamma_2 + \mu}\right) + \frac{\nu\mu}{\gamma_2 + \mu}\right) + \frac{\sigma\beta\nu\mu}{A(\gamma_1 + \mu)} = 0 \tag{4.10}$$

By rearranging Equation (4.6) for β and substituting into the above equation we gain:

$$\begin{aligned} R_0 = \max \Bigg(& \frac{1}{2x^*(q(\lambda^*)\gamma_1\alpha + D)(\gamma_2 + \mu)} \\ & \times [D(\gamma_2 + \mu + f\gamma_1\alpha + \nu\mu x^*) + \nu\mu x^* q(\lambda^*)\gamma_1\alpha \\ & \pm \left((D(f\gamma_1\alpha + \nu\mu x^* - (\gamma_2 + \mu)) + \nu\mu x^* q(\lambda^*)\gamma_1\alpha)^2 + 4D^2(\gamma_2 + \mu)f\gamma_2\alpha\right)^{\frac{1}{2}}\Big] \Bigg) \end{aligned} \tag{4.11}$$

We can differentiate Equation (4.11) with respect to x^*, but in this form it is hard to draw any conclusions. Instead, we look at $\frac{dR_0}{dx^*} = \frac{dR_0}{d\beta}\frac{d\beta}{d\lambda^*}\frac{d\lambda^*}{dx^*}$. If we can show that $\frac{dR_0}{d\beta} \neq 0$ and $\frac{d\lambda^*}{dx^*} \neq 0$, then $\frac{dR_0}{dx^*} = 0$ when $\frac{d\beta}{d\lambda^*} = 0$. We can see the relationship between the four variables R_0, x, λ and β at the steady state numerically in Figure 4.3 for varying values of f.

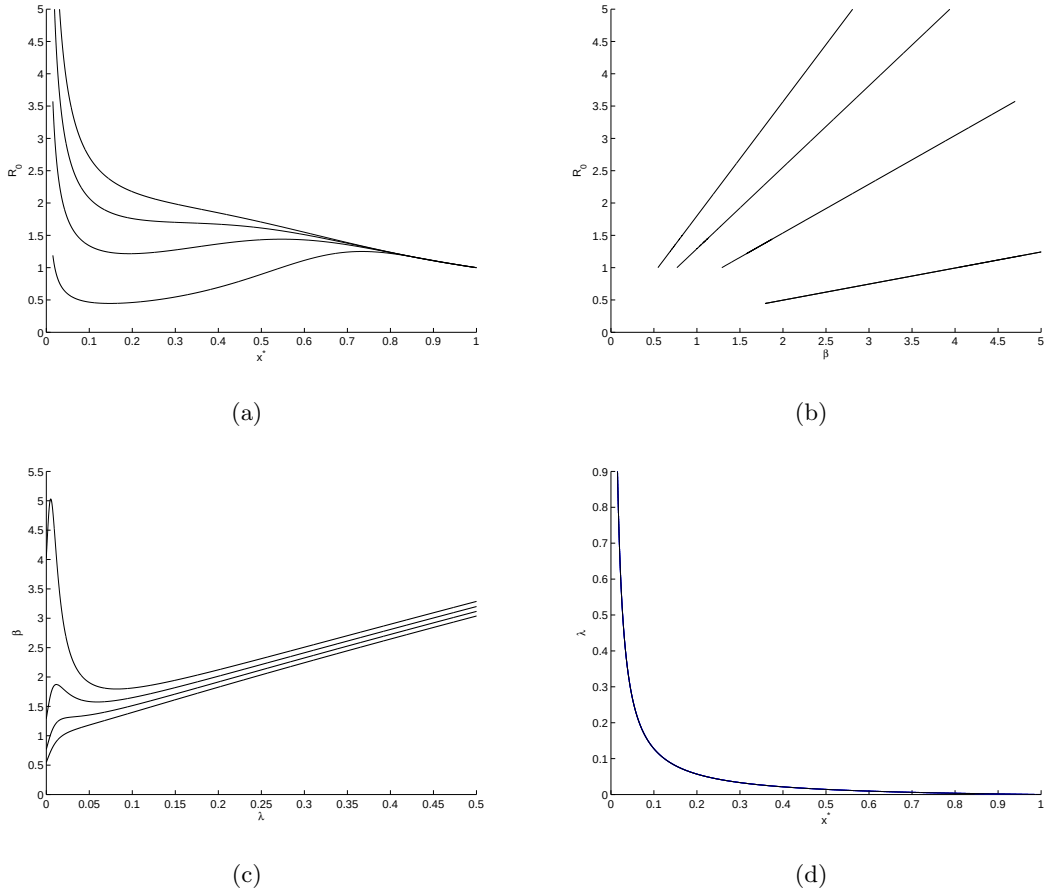


Figure 4.3: Steady state values for $f = 0; 0.02; 0.04; 0.06$. Figure (a) shows R_0 against the proportion of susceptibles in the population at the steady state, x^*, with the value of f increasing from 0 to 0.06 from the lowest to highest curve; Figure (b) shows R_0 versus β, where the value of f increases from the lowest to highest curves; Figure (c) shows β versus λ, with the value of f decreasing from the lowest to the highest curve - where the top two curves have maximums that correspond to the backwards bifurcations shown in Figure 4.1; Figure (d) shows λ versus the proportion susceptible which does not vary for changes in f.

To express R_0 in terms of β, we simply take the largest root of the characteristic equation of our next generation matrix:

$$\begin{aligned} R_0 = \max\Bigg(&\frac{1}{2A(\gamma_2+\mu)}\left(\sigma\beta(\gamma_2+\mu+f\gamma_1\alpha)+\nu\mu A\right. \\ &\left.\pm\left[(\sigma\beta(\gamma_2+\mu+f\gamma_1\alpha)+\nu\mu A)^2-4A\sigma\beta\nu\mu(\gamma_2+\mu)\right]^{\frac{1}{2}}\right)\Bigg) \end{aligned} \tag{4.12}$$

We always take R_0 to be the largest root of the quadratic given in Equation (4.12), and we know that this will always yield a positive, real value. Note that the square root part of the definition of R_0 will only be zero when:

$$\begin{aligned} &(\sigma\beta(\gamma_2+\mu+f\gamma_1\alpha)+\nu\mu A)^2-4A\sigma\beta\nu\mu(\gamma_2+\mu)=0 \\ \Rightarrow \sigma\beta &= \frac{\nu\mu A(\gamma_2+\mu-f\gamma_1\alpha)\pm\nu\mu A\sqrt{-4f\gamma_2\alpha(\gamma_2+\mu)})}{(\gamma_2+\mu+f\gamma_2\alpha)^2} \end{aligned} \tag{4.13}$$

As R_0 is a real value, this can only occur if ν, f or α are zero (as μ, γ_1 and A are all non-zero parameters). As we are considering values at the steady state, we know from Equation (4.6) that

$$\sigma\beta = \frac{A(\gamma_2+\mu-\nu\mu\omega)}{x^*(\gamma_2+\mu-\nu\mu\omega+q(\lambda)\gamma_1\alpha)} \tag{4.14}$$

If $\nu = 0$, then Equation (4.13) gives $\sigma\beta = 0$, but we know from Equation (4.14) that $\sigma\beta \neq 0$. So the case $\nu = 0$ is not a possible solution.

If $\alpha = 0$, then Equation (4.13) gives $\sigma\beta = \frac{\nu\mu A}{\gamma_2+\mu}$. Substituting this into Equation 4.14 we gain:

$$x^* = \frac{\gamma_2+\mu}{\nu\mu} > \frac{\mu}{\nu\mu} > \frac{1}{\nu} \tag{4.15}$$

As ν is a proportion, we know that it less than or equal to one. So we have a contradiction, as $x^* < 1$ - so $\alpha = 0$ is not a possible solution.

If $f = 0$, then Equation (4.13) gives $\sigma\beta = \frac{\nu\mu A}{\gamma_2+\mu}$, substituting this in Equation (4.14) we have:

$$\nu\mu x^* = \frac{(\gamma_2+\mu-\nu\mu\omega)(\gamma_2+\mu)}{(q(\lambda^*)\gamma_1\alpha+\gamma_2+\mu-\nu\mu\omega)} \tag{4.16}$$

which is a possible solution.

We want to find if $\frac{dR_0}{d\beta} = 0$. When $f = 0$ (and we know a bifurcation occurs), we have $R_0 = \frac{\sigma\beta}{(\sigma+\mu)(\gamma_1+\mu)}$, which is non-zero (even in the case where $\sigma\beta = \frac{\nu\mu A}{\gamma_2+\mu}$). When $f \neq 0$ we solve the following, letting $\frac{dR_0}{d\beta} = 0$:

$$\begin{aligned} \frac{dR_0}{d\beta} =& \frac{1}{2A(\gamma_2+\mu)}\left[\sigma(\gamma_2+\mu+f\gamma_1\alpha)\right. \\ &\left.+\frac{\sigma(\gamma_2+\mu+f\gamma_1\alpha)(\sigma\beta(\gamma_2+\mu+f\gamma_1\alpha)+\nu\mu A)-2A\sigma\nu\mu(\gamma_2+\mu)}{\sqrt{(\sigma\beta(\gamma_2+\mu+f\gamma_1\alpha)+\nu\mu A)^2-4A\sigma\beta\nu\mu(\gamma_2+\mu)}}\right] \end{aligned} \tag{4.17}$$

The parameters σ, A and $\gamma_2 + \mu$ are all non-zero, as is the square root term (as shown earlier), so we have:

$$\begin{aligned}(\gamma_2 + \mu + f\gamma_1\alpha)\sqrt{(\sigma\beta(\gamma_2 + \mu + f\gamma_1\alpha) + \nu\mu A)^2 - 4A\sigma\beta\nu\mu(\gamma_2 + \mu)} \\ = \nu\mu A(\gamma_2 + \mu + f\gamma_1\alpha) - \sigma\beta(\gamma_2 + \mu_f\gamma_1\alpha)^2\end{aligned}$$

$\Rightarrow$

$$\begin{aligned}&(\gamma_2 + \mu + f\gamma_1\alpha)^2((\sigma\beta)^2(\gamma_2 + \mu + f\gamma_1\alpha)^2 - 2\nu\mu A(\gamma_2 + \mu - f\gamma_1\alpha) + (\nu\mu A)^2) \\ &\quad = (\nu\mu A)^2(\gamma_2 + \mu - f\gamma_1\alpha)^2 \\ &\qquad - 2\nu\mu A\sigma\beta(\gamma_2 + \mu - f\gamma_1\alpha)(\gamma_2 + \mu + f\gamma_1\alpha)^2 + (\sigma\beta)^2(\gamma_2 + \mu + f\gamma_1\alpha)^2\end{aligned}$$

$\Rightarrow$

$$(\nu\mu A)^2(\gamma_2 + \mu - f\gamma_1\alpha)^2 = (\nu\mu A)^2(\gamma_2 + \mu + f\gamma_1\alpha)^2 \tag{4.18}$$

Equation (4.18) can only be true if f, γ_1 or α are zero. We stated at the beginning that we are dealing with the $f \neq 0$ case, and γ_1 is non-zero parameter. Substituting $\alpha = 0$ into our equation for $\frac{dR_0}{d\beta}$ (Equation (4.17)), we gain a non-zero result. Therefore, $\frac{dR_0}{d\beta} \neq 0$.

To show that $\frac{d\lambda^*}{dx^*} \neq 0$, we first calculate λ at the steady state, using Equations (4.5) and (4.7):

$$\begin{aligned}\lambda^* = &\quad \beta(y^* + \alpha c^*) \\ = &\quad \tfrac{\alpha\beta A\mu(x^* - \omega)}{x^*\beta(\sigma\mu\omega\nu - \alpha A) - \mu\omega\nu A}\end{aligned} \tag{4.19}$$

As λ is the force of infection, we know that it is positive, giving us:

$$\beta\sigma\mu\omega\nu - A\alpha\beta > \frac{A\mu\omega\nu}{x^*} \tag{4.20}$$

Differentiating Equation (4.19) with respect to x^*:

$$\frac{d\lambda}{dx^*} = \frac{\alpha\beta A\mu[\beta\omega(\sigma\mu\omega\nu - \alpha A) - \mu\omega\nu A]}{(x^*\beta(\sigma\mu\omega\nu - \alpha A) - \mu\omega\nu A)^2} \tag{4.21}$$

For $\frac{d\lambda}{dx^*} \leq 0$ we would need:

$$\beta\sigma\mu\omega\nu - A\alpha\beta \leq A\nu\mu \tag{4.22}$$

Using Equation (4.20) that gives:

$$\begin{aligned}\frac{A\mu\omega\nu}{x^*} < \beta\sigma\mu\omega\nu - A\alpha\beta \leq A\mu\nu \\ \Rightarrow \frac{\omega}{x^*} < 1 \\ \Rightarrow \omega < x^*\end{aligned} \tag{4.23}$$

Recalling that $1 - \omega$ is the proportion of births who are successfully immunized, so ω is essentially the proportion of unsuccessfully immunized births, and hence susceptible to

infection[1] - it is not possible to have $x^* > \omega$. Thus, $\frac{d\lambda^*}{dx^*} > 0$, as shown in Figure 4.3(d). Therefore, we must have $\frac{dR_0}{dx} = 0$ when $\frac{d\lambda}{d\beta} = 0$.

To find β in terms of λ, we rearrange Equation (4.9) for β:

$$\beta = \frac{\lambda^*(AD + \mu\omega\nu\sigma q(\lambda^*)\gamma_1) + AD\mu}{\mu\omega\sigma(q(\lambda^*)\gamma_1\alpha + D)} \tag{4.24}$$

Differentiating with respect to λ at the steady state:

$$\begin{aligned}\frac{d\beta}{d\lambda^*} = \frac{1}{\mu\omega\sigma(q(\lambda)\gamma_1\alpha + D)} \Big[& AD(q(\lambda)\gamma_1\alpha + D) + \mu\omega\nu\sigma q(\lambda)\gamma_1(q(\lambda)\gamma_1\alpha + D) \\ & + \{\lambda\nu\gamma_1\mu\omega\sigma(q(\lambda)\gamma_1\alpha + D) - \gamma_1\alpha\lambda(AD + \mu\nu\omega\sigma q(\lambda)\gamma_1) - AD\gamma_1\alpha\mu\} \frac{dq(\lambda)}{d\lambda} \Big]\end{aligned} \tag{4.25}$$

Therefore, $\frac{d\beta}{d\lambda^*} = 0$ when the following quadratic in $q(\lambda^*)$ is satisfied:

$$\begin{aligned}0 = & q^2\gamma_1^2\alpha\mu\omega\nu\sigma + q\gamma_1 D(A\alpha + \mu\omega\nu\sigma) \\ & + AD^2 + \frac{dq}{d\lambda}\gamma_1 D(\lambda\nu\mu\omega\sigma - A\alpha(\lambda + \mu))\end{aligned} \tag{4.26}$$

Thus, a bifurcation occurs when the following is satisfied (as shown in Figure 4.4):

$$q_{bif} = \frac{D(A\alpha + \nu\omega\mu\sigma}{2\gamma_1\alpha\sigma\nu\mu\omega} \left\{ -1 + \sqrt{1 - \frac{4\alpha\sigma\nu\mu\omega}{D(A\alpha + \mu\nu\omega\sigma)^2}(AD - \gamma_1(A\alpha\mu + \lambda(A\alpha - \nu\mu\omega\sigma)))\frac{dq}{d\lambda}} \right\} \tag{4.27}$$

If the function $q(\lambda)$ at the steady state is the same as q_{bif} given in Equation (4.27) then a bifurcation will occur in the R_0 versus $1 - x^*$ plane. Note that the analysis of this condition is independent of the definition of the function $q(\lambda)$ given by Medley *et al.*; any function $q(\lambda)$ that satisfies Equation 4.27 will produce a backwards bifurcation.

The unstable equilibrium of Medley *et al.* is extremely sensitive to the values of the two parameters f and α, relating to the probability that an adult will become a carrier and the relative infectiousness of a carrier. The probability of an adult developing carriage needs to be very low ($0 < f < 0.04$), and $\alpha > 0.2$ to cause a bifurcation. There is little information available on the infectiousness of carriers relative to infected individuals - however α is something that could be affected by a vaccination program. For f to be less than 0.04 would require the average age at infection to be greater than 34 years (by substituting 0.04 into the $p(a)$ equation presented in Edmunds *et al.* (1993)).

[1] We can also show that $x^* < \omega$ from the steady state of the differential equation: $\frac{dx}{dt} = -(\lambda + \mu) + \mu\omega(1 - \nu c) = 0$, so $x^* = \omega\frac{\mu}{\lambda+\mu}(1 - \nu c)$. It is clear that $\frac{\mu}{\lambda+\mu}$ is less than one, and as ν is a proportion, $(1 - \nu c) < 1$, thus $x^* < \omega$

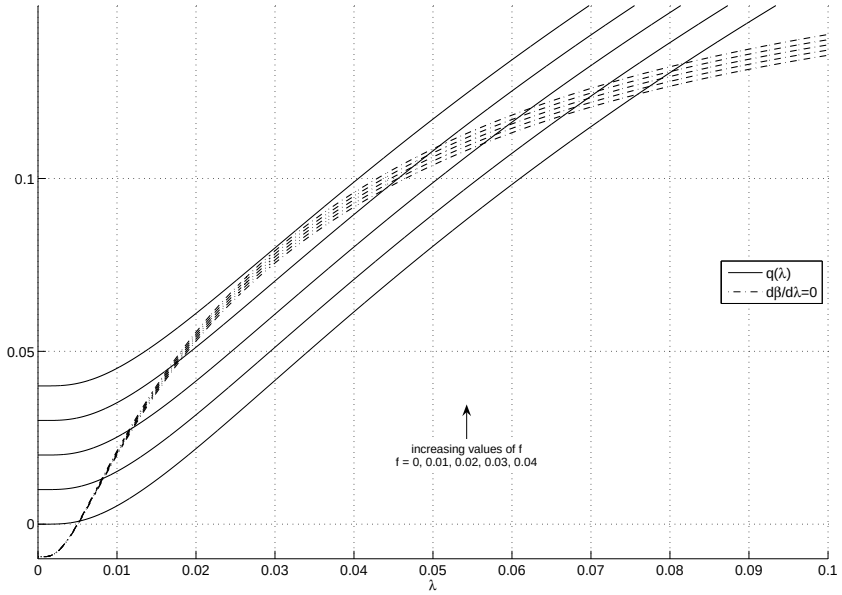


Figure 4.4: For increasing values of f ($f = 0, 0.01, ..., 0.04$, $f = 0$ produces the bottom curves), $q(\lambda)$ is shown as the solid line, and the condition for $\frac{d\beta}{d\lambda} = 0$ (Equation (4.27)) is shown as a dotted line. Where the two curves intercept is the location of the bifurcation points, and the backwards bifurcation. When f is slightly less than 0.04, the two curves no longer intercept, hence a bifurcation does not occur. For this diagram $\alpha = 1$ and $\omega = 1$.

4.4 Extending the Medley *et al.* model to multiple age classes.

We now extend the Medley *et al.* (2001) model by discretising the population into age classes and allocate each age class a probability q_i of developing the carriage state (given infection) that we can vary.

4.4.1 SEICR Model with two population classes.

For our first model we split the population into two age groups: children (aged 0–15 years) and adults (older than 15 years). We then have the following compartments for each of the age groups: susceptible, exposed (but not yet infectious), infectious, carrier (asymptomatic) and removed. Infectious individuals are those who are positive for HBsAg and HBeAg; chronically infected carriers will have been positive for HBsAg, HBeAg and Anti-HBc for longer than six months; and removed individuals are those who test positive for Anti-HBs and Anti-HBc antigens (Juszczyk, 2000; The Hepatitis Foundation of New Zealand, 2007). Children and adults both move from their susceptible compartment to the exposed compartment, then on into the infectious compartment. From being infectious, both children and adults can either become carriers or become removed (and immune from Hepatitis B). After being a carrier, you can only become removed. Children also move from S, E, I, C and R compartments to the corresponding adult compartments, as shown in Figure 4.5. We have inflow to the childhood population through the susceptible and carrier compartments. We use the model given in Medley *et al.* (2001) as a base, and adapt it to include a structured population.

$$
\begin{aligned}
\text{children} \quad & \begin{cases}
\frac{dS_c}{dt} = (1-\nu\frac{C_a}{N_a})B - (\lambda+\mu_c)S_c \\
\frac{dE_c}{dt} = \lambda S_c - (\sigma+\mu_c)E_c \\
\frac{dI_c}{dt} = \sigma E_c - (\gamma_1+\mu_c)I_c \\
\frac{dC_c}{dt} = \nu\frac{C_a}{N_a}B + q_1\gamma_1 I_c - (\gamma_2+\mu_c)C_c \\
\frac{dR_c}{dt} = (1-q_1)\gamma_1 I_c + \gamma_2 C_c - \mu_c R_c
\end{cases} \\
\text{adults} \quad & \begin{cases}
\frac{dS_a}{dt} = \mu_c S_c - (\lambda+\mu_a)S_a \\
\frac{dE_a}{dt} = \mu_c E_c + \lambda S_a - (\sigma+\mu_a)E_a \\
\frac{dI_a}{dt} = \mu_c I_c + \sigma E_a - (\gamma_1+\mu_a)I_a \\
\frac{dC_a}{dt} = \mu_c C_c + q_2\gamma_1 I_a - (\gamma_2+\mu_a)C_a \\
\frac{dR_a}{dt} = \mu_c R_c + (1-q_2)\gamma_1 I_a + \gamma_2 C_a - \mu_a R_a
\end{cases}
\end{aligned}
\tag{4.28}
$$

The force of infection, λ, is dependent on the infectious and carrier populations. We assume that infection is more likely to happen from contact with an infectious person than with a carrier, so we have

$$
\lambda = \frac{\beta}{N_c+N_a}(I_a + I_c + \alpha(C_a+C_c)) \tag{4.29}
$$

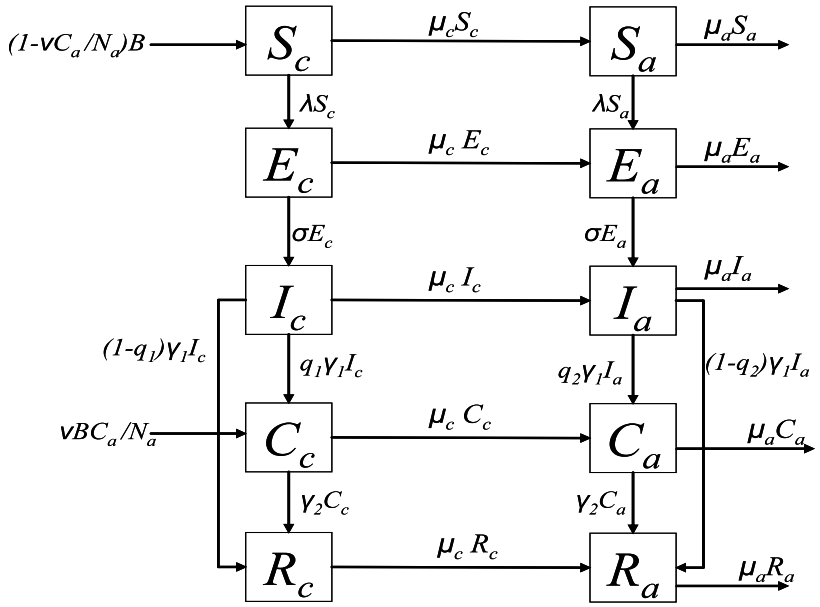


Figure 4.5: Flow chart to show the infection course for Hepatitis B when the population is split into two age groups: children and adults. There are births into both the susceptible and carrier children populations.

where N_c is the number of children in the population, and N_a is the number of adults in the population, and $\alpha < 1$ (assuming that carriers are less infective than acutely infected people).

A proportion, ν, of children born to carrier mothers become carriers. The proportion of infected individuals that go on to become carriers depends on the age at infection, with $q_1 > q_2$. We have ignored deaths in the child age group, but have allowed a natural death rate from the adult compartments, and have assumed that the recovery and viral progression rates are the same for both age groups. The transmission coefficient, β, has units per year and B is a constant birth rate per year. The rate at which children become adults is μ_c ($=\frac{1}{15}$ per year, i.e. they remain children for an average of 15 years), and is the rate at which adults die is μ_a ($=\frac{1}{55}$ per year, i.e. they remain adults for an average of 55 years). The rate at which those exposed become infected is σ, the rate at which those infected leave the compartment to become either carriers or immune is γ_1 , and the rate at which carriers become removed is γ_2.

We calculate R_0 from the largest value of the next generation matrix, which is constructed as follows — there are three types of infection: horizontally infected children; horizontally infected adults, and born carriers. Figure 4.6 shows the proportions of each host type that move on to the next host type. Only infected and carrier adults and children are able to infect others. Infected children infect $\frac{\beta}{(N_a+N_c)(\gamma_1+\mu_c)}$ people, infected adults infect $\frac{\beta}{(N_a+N_c)(\gamma_1+\mu_a)}$, carrier children infect $\frac{\alpha\beta}{(N_a+N_c)(\gamma_2+\mu_c)}$ and carrier adults infect $\frac{\alpha\beta}{(N_a+N_c)(\gamma_2+\mu_a)}$.

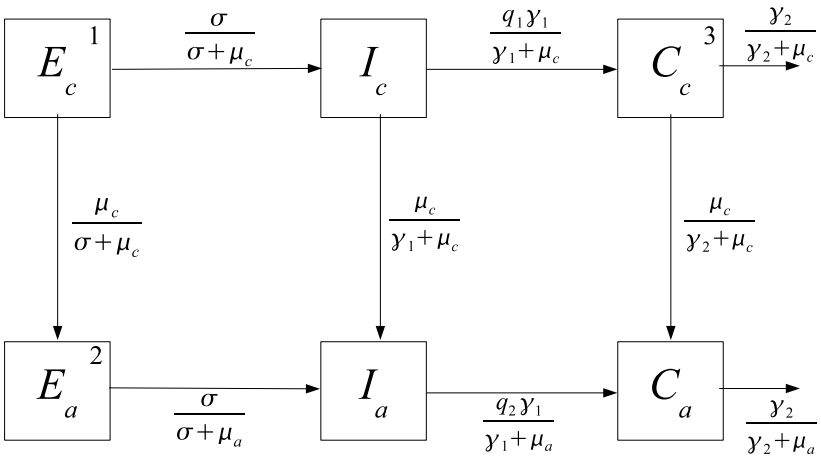


Figure 4.6: The movement between the infected compartments, used for constructing the next generation matrix. From the carrier compartments, individuals become removed and are no longer infected. The three types in infection are noted with the superscripts: 1) horizontally infected children, 2) horizontally infected adults and 3) born carrier children (or vertically infected children).

We construct a 3x3 matrix to show the infection interactions between these types.

$K_{1,1}$: *horizontally infected children to horizontally infected children*: Horizontally infected children start in the E_c compartment. In order to infect other children they have to become either: 1) infected children; 2) infected adults; 3) carrier children or 4) carrier adults.

1) A proportion $\frac{\sigma}{\sigma+\mu_c}$ of exposed children go on to become infected children, who will infect $\frac{\beta N_c}{(\gamma_1+\mu_c)(N_a+N_c)}$ others.

2) For exposed children to become infected adults, they must first either become infected children ($\frac{\sigma}{\sigma+\mu_c}\frac{\mu_c}{\gamma_1+\mu_c}$) or exposed adults ($\frac{\mu_c}{\sigma+\mu_c}\frac{\sigma}{\sigma+\mu_c}$). The number of children they then go on to infect is $\frac{\beta N_c}{(\gamma_1+\mu_a)(N_a+N_c)}$.

3) The proportion of exposed children who become infected children, then carrier children is $\frac{\sigma}{\sigma+\mu_c}\frac{q_1\gamma_1}{\gamma_1+\mu_c}$. They then go on to infect $\frac{\alpha\beta N_c}{(\gamma_2+\mu_c)(N_a+N_c)}$ children.

4) There are three ways for exposed children to become carrier adults: a proportion of exposed children will first become infected, then carrier children and then finally carrier adults, $\frac{\sigma}{\sigma+\mu_c}\frac{q_1\gamma_1}{\gamma_1+\mu_c}\frac{\mu_c}{\gamma_2+\mu_c}$; a proportion will become infected children, then infected adults then carrier adults, $\frac{\sigma}{\sigma+\mu_c}\frac{\mu_c}{\gamma_1+\mu_c}\frac{q_2\gamma_1}{\gamma_1+\mu_a}$; and a proportion will become exposed adults, then infected and carrier adults, $\frac{\mu_c}{\sigma+\mu_c}\frac{\sigma}{\sigma+\mu_a}\frac{q_2\gamma_1}{\gamma_1+\mu_a}$. Carrier adults will then infect $\frac{\alpha\beta N_c}{(\gamma_2+\mu_a)(N_a+N_c)}$ children.

Putting these four components together we have the first entry in the next generation matrix:

$$\begin{aligned}
K_{1,1} &= \frac{\sigma}{\sigma+\mu_c}\frac{\beta N_c}{(\gamma_1+\mu_c)(N_a+N_c)} \\
&+ \left(\frac{\sigma}{\sigma+\mu_c}\frac{\mu_c}{\gamma_1+\mu_c}+\frac{\mu_c}{\sigma+\mu_c}\frac{\sigma}{\sigma+\mu_a}\right)\frac{\beta N_c}{(\gamma_1+\mu_a)(N_c+N_a)} \\
&+ \frac{\sigma}{\sigma+\mu_c}\frac{q_1\gamma_1}{\gamma_1+\mu_c}\frac{\alpha\beta N_c}{(\gamma_1+\mu_c)(N_c+N_a)} \\
&+ \left(\frac{\sigma}{\sigma+\mu_c}\frac{q_1\gamma_1}{\gamma_1+\mu_c}\frac{\mu_c}{\gamma_2+\mu_c}+\frac{\sigma}{\sigma+\mu_c}\frac{\mu_c}{\gamma_1+\mu_c}\frac{q_2\gamma_1}{\gamma_1+\mu_a}\right. \\
&+ \left.\frac{\mu_c}{\sigma+\mu_c}\frac{\sigma}{\sigma+\mu_a}\frac{q_2\gamma_1}{\gamma_1+\mu_a}\right)\frac{\alpha\beta N_c}{(\gamma_2+\mu_a)(N_c+N_a)}
\end{aligned}$$

$K_{1,2}$: *horizontally infected adults to horizontally infected children*: Exposed adults can infect children when they become infected or carrier adults. The number of children infected by exposed adults that become infected adults is $\frac{\sigma}{\sigma+\mu_a}\frac{\beta N_c}{(\gamma_1+\mu_a)(N_a+N_c)}$, and the number of children who are infected by exposed adults who have become carrier adults is $\frac{\sigma}{\sigma+\mu_a}\frac{q_2\gamma_1}{\gamma_1+\mu_a}\frac{\alpha\beta N_c}{(\gamma_2+\mu_a)(N_a+N_c)}$. Hence

$$K_{1,2} = \frac{\sigma\beta}{(\sigma+\mu_a)(\gamma_1+\mu_a)}\left(1+\frac{\alpha q_2\gamma_1}{\gamma_2+\mu_a}\right)\frac{N_c}{N_a+N_c}$$

$K_{1,3}$: *born carriers to horizontally infected children*: Born carriers either infect children directly, $\frac{\alpha\beta N_c}{\gamma_2+\mu_c}$, or they go to to become carrier adults and infect $\frac{\mu_c}{\gamma_2+\mu_c}\frac{\alpha\beta N_c}{\gamma_2+\mu_a}$ children. Thus

$$K_{1,3} = \frac{\alpha\beta}{\gamma_2+\mu_c}\left(1+\frac{\mu_c}{\gamma_2+\mu_a}\right)\frac{N_c}{N_a+N_c}$$

$K_{2,1}$: *horizontally infected children to horizontally infected adults*: Horizontally infected children create horizontally infected adults in exactly the same manner as they create horizontally infected children, but the number of adults they infect will depend on N_a rather than N_c. So $K_{2,1} = K_{1,2}\frac{N_a}{N_c}$.

$$\begin{aligned}
K_{2,1} &= \frac{\sigma}{\sigma+\mu_c}\frac{\beta N_a}{(\gamma_1+\mu_c)(N_a+N_c)} \\
&+ \left(\frac{\sigma}{\sigma+\mu_c}\frac{\mu_c}{\gamma_1+\mu_c}+\frac{\mu_c}{\sigma+\mu_c}\frac{\sigma}{\sigma+\mu_a}\right)\frac{\beta N_a}{(\gamma_1+\mu_a)(N_c+N_a)} \\
&+ \frac{\sigma}{\sigma+\mu_c}\frac{q_1\gamma_1}{\gamma_1+\mu_c}\frac{\alpha\beta N_a}{(\gamma_1+\mu_c)(N_c+N_a)} \\
&+ \left(\frac{\sigma}{\sigma+\mu_c}\frac{q_1\gamma_1}{\gamma_1+\mu_c}\frac{\mu_c}{\gamma_2+\mu_c}+\frac{\sigma}{\sigma+\mu_c}\frac{\mu_c}{\gamma_1+\mu_c}\frac{q_2\gamma_1}{\gamma_1+\mu_a}\right. \\
&+ \left.\frac{\mu_c}{\sigma+\mu_c}\frac{\sigma}{\sigma+\mu_a}\frac{q_2\gamma_1}{\gamma_1+\mu_a}\right)\frac{\alpha\beta N_a}{(\gamma_2+\mu_a)(N_c+N_a)}
\end{aligned}$$

$K_{2,2}$: *horizontally infected adults to horizontally infected adults*: Horizontally infected adults can go on to become infected adults, and they will infect $\frac{\sigma}{\sigma+\mu_a}\frac{\beta N_a}{(\gamma_1+\mu_a)(N_a+N_c)}$ other adults. From being infected adults, a number will of these will go on to become carrier adults and will infect $\frac{\sigma}{\sigma+\mu_a}\frac{q_2\gamma_1}{\gamma_1+\mu_a}\frac{\alpha\beta N_a}{(\gamma_2+\mu_a)(N_a+N_c)}$ more adults. Therefore,

$$K_{2,2} = \frac{\sigma\beta}{(\sigma+\mu_a)(\gamma_1+\mu_a)}\left(1+\frac{\alpha q_2\gamma_1}{\gamma_2+\mu_a}\right)\frac{N_a}{N_a+N_c}$$

$K_{2,3}$: *born carriers to horizontally infected adults*: A born carrier will infect other adults in the same was as they infect children, but the rates of infection will be multiplied by N_a rather than N_c. Accordingly,

$$K_{2,3} = \frac{\alpha\beta}{\gamma_2+\mu_c}\left(1+\frac{\mu_c}{\gamma_2+\mu_a}\right)\frac{N_a}{N_a+N_c}$$

$K_{3,1}$: *horizontally infected children to born carriers*: Horizontally infected children can only give rise to born carriers by first becoming carrier adults, which they can do in three ways: 1) by becoming an infected child, carrier child then carrier adults; 2) by becoming an infected child, then adult, then a carrier adults, and 3) by becoming an exposed, infected then carrier adult. Once the carrier adult status is reached, the number of born carriers produced is $\frac{\nu B}{N_a(\gamma_2+\mu_a)}$.

1) The number of exposed children who become an infected child, carrier child, then carrier adult is $\frac{\sigma}{\sigma+\mu_c}\frac{q_1\gamma_1}{\gamma_1+\mu_c}\frac{\mu_c}{\gamma_2+\mu_c}$.

2) The number of exposed children who become an infected child, then adults, then a carrier adult is $\frac{\sigma}{\sigma+\mu_c}\frac{\mu_c}{\gamma_1+\mu_c}\frac{q_2\gamma_1}{\gamma_1+\mu_a}$.

3) The number of exposed children who become an exposed, infected than carrier adult is $\frac{\mu_c}{\sigma+\mu_c}\frac{\sigma}{\sigma+\mu_a}\frac{q_2\gamma_1}{\gamma_1+\mu_a}$.

Combining these:

$$K_{3,1} = \frac{\nu\gamma_1\mu_c\sigma}{(\gamma_2+\mu_a)(\sigma+\mu_c)}\left(\frac{q_1}{(\gamma_1+\mu_c)(\gamma_2+\mu_c)} + \frac{q_2}{(\gamma_1+\mu_c)(\gamma_1+\mu_a)} + \frac{q_2}{(\sigma+\mu_a)(\gamma_1+\mu_a)}\right)\frac{B}{N_a}$$

$K_{3,2}$: *horizontally infected adults to to born carriers*: A proportion , $\frac{\sigma}{\sigma+\mu_a}\frac{q_2\gamma_1}{\gamma_1+\mu_a}$, of exposed adults go on to become carrier adults, who then create $\frac{\nu B}{N_a(\gamma_2+\mu_a)}$ born carriers. It follows that

$$K_{3,2} = \frac{\sigma q_2\gamma_1\nu}{(\sigma+\mu_a)(\gamma_1+\mu_a)(\gamma_2+\mu_a)}\frac{B}{N_a}$$

$K_{3,3}$: *born carriers to born carriers*: A proportion of born carriers become adult carriers, $\frac{\mu_c}{\gamma_2+\mu_c}$, who then go on to give birth to carriers, $\frac{\nu B}{N_a(\gamma_2+\mu_a)}$. Giving

$$K_{3,3} = \frac{\mu_c}{\gamma_2+\mu_c}\frac{\nu}{\gamma_2+\mu_a}\frac{B}{N_a}$$

The matrix K is our next generation matrix, the largest eigenvalue of which is R_0.

To calculate the Jacobian matrix for Equations (4.28), we note that there is a redundancy as the population remains constant (so we omit the equations for R_c and R_a), thus the Jacobian matrix is:

$$J = \begin{pmatrix} -\lambda-\mu_c & 0 & \frac{\beta}{N_a+N_c}S_c & -\frac{\alpha\beta}{N_a+N_c}S_c \\ \lambda & -(\sigma+\mu_c) & \frac{\beta}{N_a+N_c}S_c & \frac{\alpha\beta}{N_a+N_c}S_c \\ 0 & \sigma & -(\gamma_1+\mu_c) & 0 \\ 0 & 0 & q_1\gamma_1 & \frac{\nu B}{N_a+N_c}-(\gamma_2+\mu_c) \\ \mu_c & 0 & -\frac{\beta}{N_a+N_c}S_a & -\frac{\alpha\beta}{N_a+N_c}S_a \\ 0 & \mu_c & \frac{\beta}{N_a+N_c}S_a & \frac{\alpha\beta}{N_a+N_c}S_a \\ 0 & 0 & \mu_c & 0 \\ 0 & 0 & 0 & \mu_c \end{pmatrix} \quad (4.30)$$

$$\begin{pmatrix} \dots & 0 & 0 & \frac{\beta}{N_a+N_c}S_c & -\frac{\alpha\beta}{N_a+N_c}S_c-\frac{\nu B}{N_a} \\ \dots & 0 & 0 & \frac{\beta}{N_a+N_c}S_c & \frac{\alpha\beta}{N_a+N_c}S_c \\ \dots & 0 & 0 & 0 & 0 \\ \dots & 0 & 0 & 0 & 0 \\ \dots & -(\lambda+\mu_a) & 0 & -\frac{\beta}{N_a+N_c}S_a & -\frac{\alpha\beta}{N_a+N_c}S_a \\ \dots & \lambda & -(\sigma+\mu_a) & \frac{\beta}{N_a+N_c}S_a & \frac{\alpha\beta}{N_a+N_c} \\ \dots & 0 & \sigma & -(\gamma_1+\mu_a) & 0 \\ \dots & 0 & 0 & q_2\gamma_1 & -(\gamma_2+\mu_a) \end{pmatrix}$$

We can show numerically that the eigenvalues of the Jacobian matrix at the trivial steady state ($S_c = N_c = \frac{B}{\mu_c}$, $S_a = N_a = \frac{B}{\mu_a}$, and $E_{c,a} = I_{c,a} = C_{c,a} = R_{c,a} = 0$) are all negative when $R_0 < 1$ - indicating that the trivial steady state is stable (see Figure 4.7), and that there is a positive eigenvalue when $R_0 > 1$. We can also show numerically that the Jacobian at the trivial steady state has an eigenvalue of zero when the next generation matrix has an eigenvalue of one ($R_0 = 1$).

The bifurcation diagram for this case is shown in Figure 4.8 - the trivial steady state along the zero seropositive line is not shown, but would be stable when $R_0 < 1$ (and the only steady state) then unstable afterwards. The endemic steady state is shown in the figure, and is stable when $R_0 > 1$.

We can solve this system of Equations (4.28) numerically using MATLAB. Initially letting there be one infected and one carrier adult in the population, we gain the results shown in Figure 4.9, with no vaccination. We see that the epidemic takes 50 years to reach the peak number of infectious people in the population. After this point, the number of infectious people decreases to a fairly constant level, whereas the number of carriers continues to increase for a few more years before settling to a steady state. The parameter values for this solution are the same as those used by Medley *et al.* (2001), with two death rates, a birth rate of 64460 people per year and $\alpha = 0.2$. The probability of becoming a carrier for each age group was taken as a mean value of Medley *et al.* function $q(t)$:

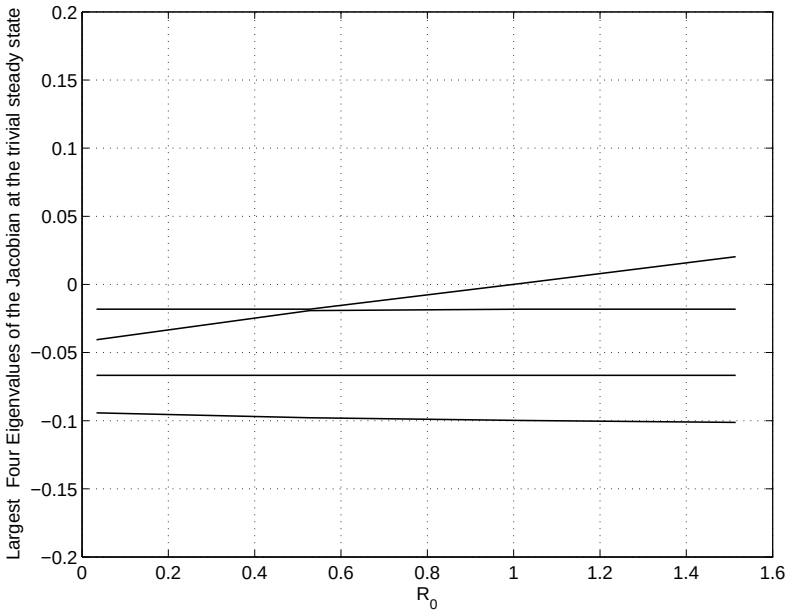


Figure 4.7: Finding the eigenvalues of the next generation matrix and the Jacobian at the trivial state for our two population model, we can see that the largest eigenvalue of the Jacobian is negative when $R_0 < 1$ and zero when $R_0 = 0$, indicating that the trivial steady state is stable.

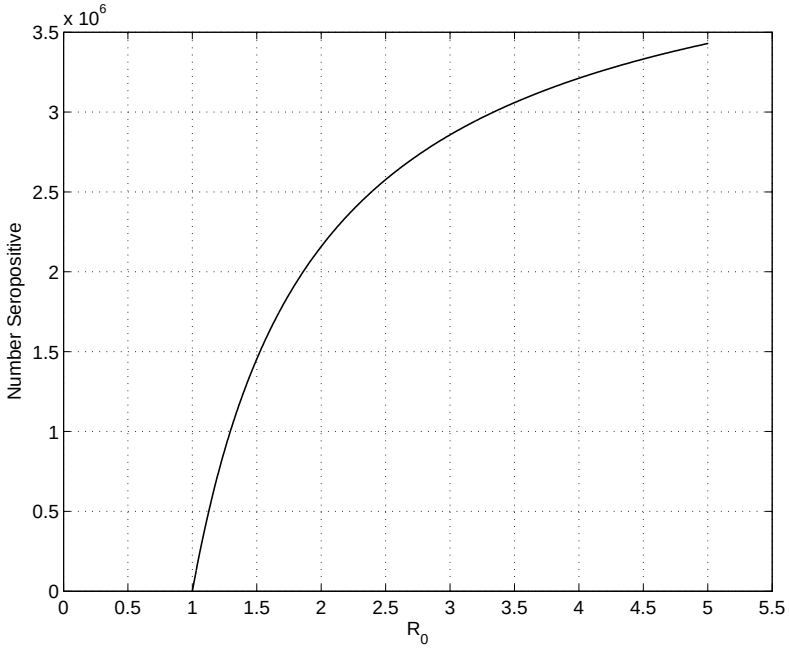
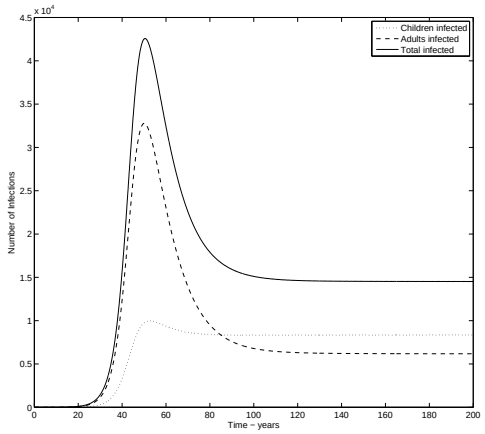
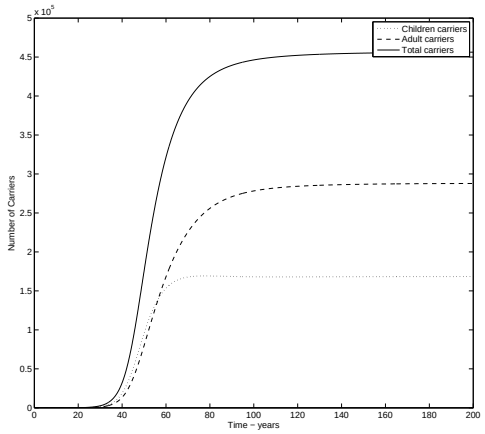


Figure 4.8: Bifurcation diagram for the two population Hepatitis model. The endemic steady state is shown, which is stable when R_0 is greater than one. A transcritical bifurcation happens when $R_0 = 1$, with the trivial steady state becoming unstable, and the endemic state appearing.



(a)



(b)

Figure 4.9: The progression of Hepatitis B in a population split into the age groups is shown. Subplot (a) shows the number of infected children, adults and total and subplot (b) shows the number of children, adults and total carriers. The epidemic takes 50 years to peak, leaving a large number of carriers and infected people in the population. The basic reproduction number is $R_0 = 3.14$ and we started the epidemic by having one carrier and one infected in the adult population.

$q_1 = (1-\exp(-0.645\times 15^{0.455}))/2 = 0.4452$ and $q_2 = (\exp(-0.645\times 15^{0.455})-\exp(-0.645\times 70^{0.455}))/2 = 0.0490$ ($f = 0$). These parameters gave us a basic reproduction ratio of 3.14.

Our results have shown that splitting the population into two age groups, and using a discrete value for the probability of becoming a carrier based on age, has not yielded the same results as Medley *et al.* (2001). Our results have also shown a very high number of infectious people in the population, even with a relatively low basic reproduction ratio of 3.14. To compare this model to known data, we first need to calculate the incidence of infection (i_c and i_a) – the number of new cases of infection per year. This is given

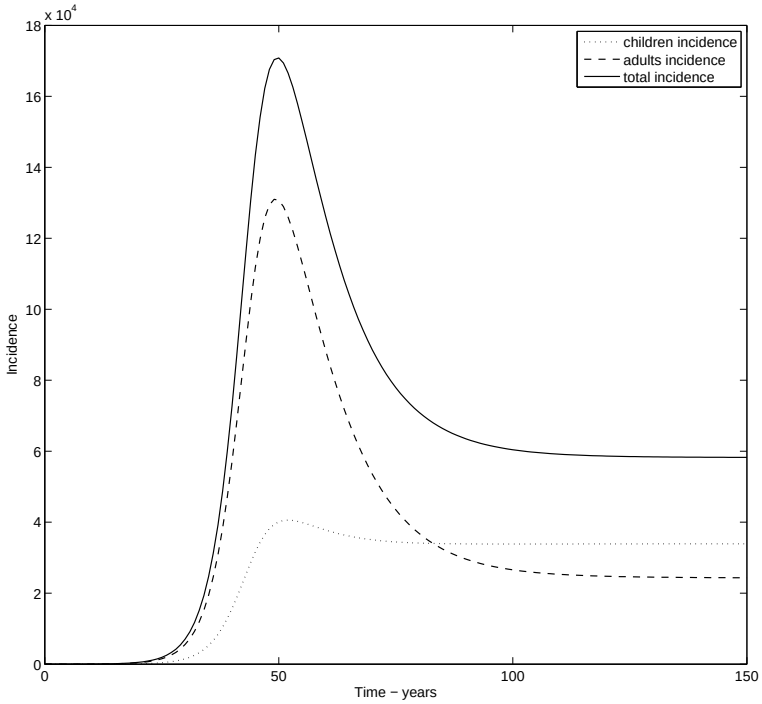


Figure 4.10: The yearly incidence of infection for the two age cohort model, with a basic reproduction ratio of 3.14 (parameter values given in text).

by: $i_c = \sigma E_c$ for the childhood population and $i_a = \sigma E_a$ for the adult population. After solving the Equations (4.28), we calculate the incidence of infection for the children and adults per year with the results shown in Figure 4.10. A peak incidence of approximately 171,000 infections per year is reached fifty years after the infection was introduced into the population, and a steady state is reached after approximately 110 years where children have a higher incidence rate than adults.

4.5 Discussion

We have shown a detailed critique of Medley *et al.* (2001), and found the conditions that are needed to gain the backwards bifurcation. Extending this model to two age classes, so a discrete value in each age group for the probability of becoming a carrier is used, did not give a backwards bifurcation. This model did produce results that we would expect for a model of Hepatitis B, with a peak in incidence of infection followed by an endemic steady state with the number of children infected higher than the number of adults infected.

Although the model by Medley *et al.* produces interesting mathematical results, it may not be the best model and parameter estimates for Hepatitis B. The model is very sensitive to initial conditions, but even with very low values of R_0 can still produce a high proportion of the population who are infected. When extended to two age groups, the

model still gives a high incidence of infection. The model presented in this chapter does not appear to be very sensitive to initial conditions, but a more robust analysis of the parameters and the initial conditions is left to future work.

The model given by Medley *et al.* is, obviously, sensitive to the two parameters f and α, with select combinations of these giving rise to the backwards bifurcation (as shown in Figure 4.2). Their model is also sensitive to other parameters (as discussed in their paper), noting that when the duration of carriage is of the same time-scale as the duration of acute infection, the backwards bifurcation does not occur. Their model is also sensitive to initial conditions.

Our two age class model captures the important aspects of the epidemiology of Hepatitis B infection in New Zealand, the model does not give the backwards bifurcations that (Medley *et al.*, 2001) gives, as we were expecting. This could be mostly due to the approximation that (Medley *et al.*, 2001) made for the proportion of infected individuals that go on to the become carriers, $q(\lambda)$, whereas our model had constant values for each age group. We found the condition that the function $q(\lambda)$ must satisfy to give the backwards bifurcation, which does not depend on the exact $q(\lambda)$ that (Medley *et al.*, 2001) used. From all the literature that we reviewed, Medley *et al.* (2001) was the only model to exhibit the backwards bifurcation. Thornley *et al.* (2008) applied the model presented by Medley *et al.* (2001) to the adult Tongan population in New Zealand, and found that the model overestimated the number of people in the infected class and the number of people who are seropositive (infected at some time in their lives, but not necessarily infectious now) in the population. With our extension to the Medley *et al.* (2001) and the results from Thornley *et al.* (2008), we are led to think that although it is an interesting model, it is not entirely suited for the accurate modelling of epidemiology of Hepatitis B virus.

Chapter 5

Modelling the Epidemiology of Hepatitis B in New Zealand

5.1 Introduction

Chapter 4 gave an introduction to the epidemiology of Hepatitis B, and a brief extension to an existing model for Hepatitis B, but did not compare this with any known data. In this chapter we shall formulate other models for Hepatitis B and fit them to New Zealand data.

Vaccination against Hepatitis B was introduced in New Zealand in 1985 where it was only offered to newborns of infected mothers. The vaccination schedule has been changed numerous times since then, with the current schedule having three doses of vaccine: at age six weeks, three months and five months. Babies born to carrier mothers receive the hepatitis B vaccine and hepatitis B immunoglobulin at birth. The vaccine will not cure chronic hepatitis, but it is 95% effective in preventing chronic infections (World Health Organisation, 2000). New Zealand as a whole is defined as a country with low endemicity of Hepatitis B (World Health Organization, 2001), but there are areas within the country with medium to high endemic levels (New Zealand Ministry of Health, 2002).

5.2 Five Age Groups with Vaccination

We start by extending our previous two age group model to include five age groups so that we can more easily include historic vaccination campaigns. Age group one is 0 – 15 months old, group 2 is 15 months – 6 years old, group 3 is 6 – 16 years old, group 4 is 16 – 45 years old, and age group 5 is the rest of the population, as shown in Equations (5.1)–(5.5). $P_i(t)$ are the proportion of each susceptible age class that are vaccinated at time t — the dependence on time allows us to vary the vaccination rates to match the known schedules. Vaccination of newborns is also dependent on time, $1-\omega(t)$, and the proportion of carrier babies born to carrier mothers is also time dependent, $\nu(t)$. Those older than

16 years are not vaccinated. Each age group has a decreasing proportion of infectives that go on to become carriers with parameter values taken from (Edmunds *et al.*, 1993), and we assume that only women from age group 4 (16 – 45 years old) are able to reproduce.

$$\text{group 1 (0–1.25 years old)} \begin{cases} \frac{dS_1}{dt} = \omega\left(1-\nu\frac{C_4}{N_4}\right)B - (\lambda_1+\mu_1)S_1 \\ \frac{dE_1}{dt} = \lambda_1 S_1 - (\sigma+\mu_1)E_1 \\ \frac{dI_1}{dt} = \sigma E_1 - (\gamma_1+\mu_1)I_1 \\ \frac{dC_1}{dt} = \omega\nu\frac{C_4}{N_4}B(t) + q_1\gamma_1 I_1 - (\gamma_2+\mu_1)C_1 \\ \frac{dR_1}{dt} = (1-\omega)B + (1-q_1)\gamma_1 I_1 + \gamma_2 C_1 - \mu_1 R_1 \end{cases} \tag{5.1}$$

$$\text{group 2 (1.25–6 years old)} \begin{cases} \frac{dS_2}{dt} = (1-P_1(t))\mu_1 S_1 - (\lambda_2+\mu_2)S_2 \\ \frac{dE_2}{dt} = \mu_1 E_1 + \lambda_2 S_2 - (\sigma+\mu_2)E_2 \\ \frac{dI_2}{dt} = \mu_1 I_1 + \sigma E_2 - (\gamma_1+\mu_2)I_2 \\ \frac{dC_2}{dt} = \mu_1 C_1 + q_2\gamma_1 I_2 - (\gamma_2+\mu_2)C_2 \\ \frac{dR_2}{dt} = \mu_1 R_1 + P_1(t)\mu_1 S_1 + (1-q_2)\gamma_1 I_2 + \gamma_2 C_2 - \mu_2 R_2 \end{cases} \tag{5.2}$$

$$\text{group 3 (6–16 years old)} \begin{cases} \frac{dS_3}{dt} = (1-P_2(t))\mu_2 S_2 - (\lambda_3+\mu_3)S_3 \\ \frac{dE_3}{dt} = \mu_2 E_2 + \lambda_3 S_3 - (\sigma+\mu_3)E_3 \\ \frac{dI_3}{dt} = \mu_2 I_2 + \sigma E_3 - (\gamma_1+\mu_3)I_3 \\ \frac{dC_3}{dt} = \mu_2 C_2 + q_3\gamma_1 I_3 - (\gamma_2+\mu_3)C_3 \\ \frac{dR_3}{dt} = \mu_2 R_2 + P_2(t)\mu_2 S_2 + (1-q_3)\gamma_1 I_3 + \gamma_2 C_3 - \mu_3 R_3 \end{cases} \tag{5.3}$$

$$\text{group 4 (16–45 years old)} \begin{cases} \frac{dS_4}{dt} = (1-P_3(t))\mu_3 S_3 - (\lambda_4+\mu_4)S_4 \\ \frac{dE_4}{dt} = \mu_3 E_3 + \lambda_4 S_4 - (\sigma+\mu_4)E_4 \\ \frac{dI_4}{dt} = \mu_3 I_3 + \sigma E_4 - (\gamma_1+\mu_4)I_4 \\ \frac{dC_4}{dt} = \mu_3 C_3 + q_4\gamma_1 I_4 - (\gamma_2+\mu_4)C_4 \\ \frac{dR_4}{dt} = P_3(t)\mu_3 S_3 + \mu_3 R_3 + (1-q_4)\gamma_1 I_4 + \gamma_2 C_4 - \mu_4 R_4 \end{cases} \tag{5.4}$$

$$\text{group 5 (45–70 years old)} \begin{cases} \frac{dS_5}{dt} = \mu_4 S_4 - (\lambda_5+\mu_5)S_5 \\ \frac{dE_5}{dt} = \mu_4 E_4 + \lambda_5 S_5 - (\sigma+\mu_5)E_5 \\ \frac{dI_5}{dt} = \mu_4 I_4 + \sigma E_5 - (\gamma_1+\mu_5)I_5 \\ \frac{dC_5}{dt} = \mu_4 C_4 + q_5\gamma_1 I_5 - (\gamma_2+\mu_5)C_5 \\ \frac{dR_5}{dt} = \mu_4 R_4 + (1-q_5)\gamma_1 I_5 + \gamma_2 C_5 - \mu_5 R_5 \end{cases} \tag{5.5}$$

where

$$\lambda_i = \frac{\beta}{\sum_{k=1}^{5} N_k} \sum_{j=1}^{5} m_{ij}(I_j + \alpha C_j) \tag{5.6}$$

$$\frac{dN}{dt} = B - \mu_5 N_5 \tag{5.7}$$

and m_{ij} are the components of a matrix representing the different contact rates between different age classes (as shown in Equation (5.8)). Values used for the mixing parameters are: $a_1 = 1$, $a_2 = 2$, $a_3 = 2$, $a_4 = 4$, $a_5 = 1$ and $\epsilon = 0.18$. Solving this numerically using MATLAB, we initially let there be one exposed and one infected person in age groups 4 and 5, and every other age group fully susceptible. We use similar parameter values to those used in the two population age group model, and gain Figure 5.1. The lowest line in both plots is for age group 1, then the second line is age groups 1 and 2, and so forth until the top line is the entire population. There is a peak in the total number of people infected before the epidemic reduces to a endemic steady state. The majority of the cases are in age group 4 (16–45 years old), but this is not entirely unexpected as this is our largest age group.

$$M = \begin{pmatrix} a_1 & \epsilon\sqrt{a_1 a_2} & \epsilon\sqrt{a_1 a_3} & \epsilon\sqrt{a_1 a_4} & \epsilon\sqrt{a_1 a_5} \\ \epsilon\sqrt{a_1 a_2} & a_2 & \epsilon\sqrt{a_2 a_3} & \epsilon\sqrt{a_2 a_4} & \epsilon\sqrt{a_2 a_5} \\ \epsilon\sqrt{a_1 a_3} & \epsilon\sqrt{a_2 a_3} & a_3 & \epsilon\sqrt{a_3 a_4} & \epsilon\sqrt{a_3 a_5} \\ \epsilon\sqrt{a_1 a_4} & \epsilon\sqrt{a_2 a_4} & \epsilon\sqrt{a_3 a_4} & a_4 & \epsilon\sqrt{a_4 a_5} \\ \epsilon\sqrt{a_1 a_5} & \epsilon\sqrt{a_2 a_5} & \epsilon\sqrt{a_3 a_5} & \epsilon\sqrt{a_4 a_5} & a_5 \end{pmatrix} \tag{5.8}$$

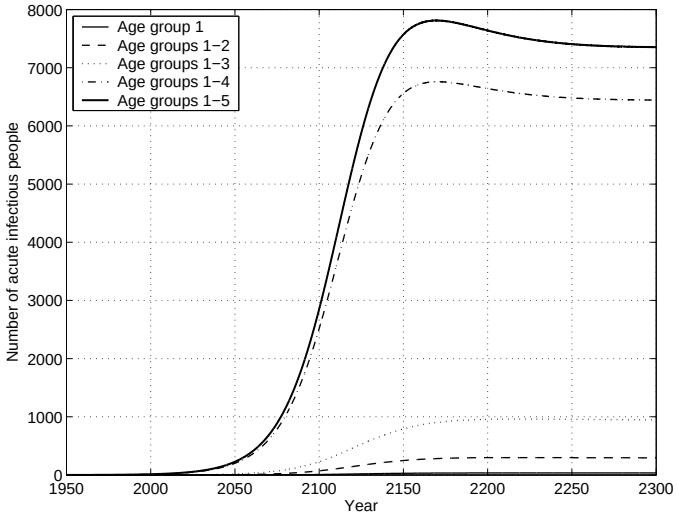
To calculate the next generation matrix for this system, we look at the proportion of people that move between compartments and the expected time they spend in each of these compartments, as shown in Figure 5.2. There are six initial types of infection – each of the exposed classes and the born carrier class. So we have a 6x6 matrix with the first row/column representing horizontally infected age group 1, the second row/column representing horizontally infected age group 2, and so on until the sixth row/column represents the born carriers. As the number of compartments is quite large, and there are numerous routes to take, we shall break the process down further. Infections only occur with contact with I_i and C_i class individuals, so we first find the rate at which people from each E_i class that get to each infected and carrier compartment.

We let ι_j^k be the proportion of exposed age class k that become age class j infectious, and let κ_j^k be the proportion of exposed age class k that become carriers in age class j. These are calculated as follows:

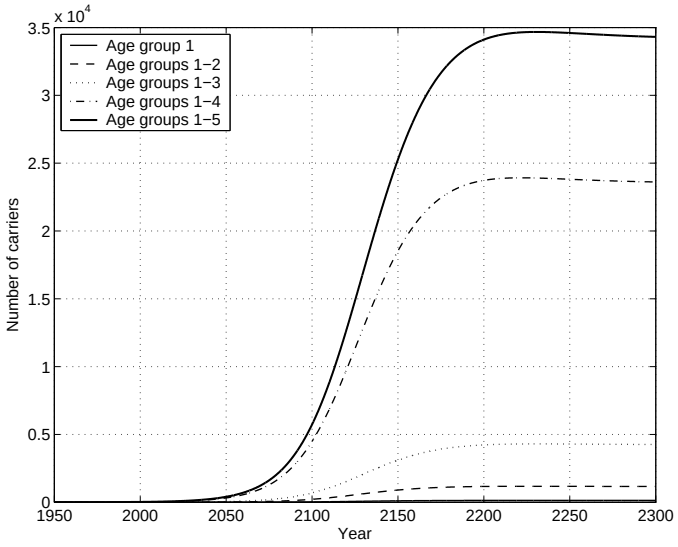
Starting from E_1 we have to consider the proportions that move to each of C_i and I_i for $i = 1..5$. We use a single arrow to denote a direct movement between compartments/age classes, and a double arrow to imply that there are multiple routes. Thus, we have:

- To become an I_1 from E_1: $(E_1 \to I_1)$.

$$\iota_1^1 = \frac{\sigma}{\sigma + \mu_1}$$



(a)



(b)

Figure 5.1: The number of people infected (a) and becoming carriers (b) in each age class of the population. The parameter values used to generate this taken from (Medley *et al.*, 2001), with our q_i values taken as an average of the function $p(a) = \exp(-0.645a^{0.455})$ from (Edmunds *et al.*, 1993). The epidemic started in 1950 with a one carrier and one acutely infected in age class 4, with $R_0 = 1.5$.

- To become a C_1 from E_1: $(E_1 \to I_1 \to C_1)$

$$\kappa_1^1 = \iota_1^1 \frac{q_1\gamma_1}{\gamma_1 + \mu_1}$$

- To become an I_2 from E_1: $(E_1 \to E_2 \to I_2$ and $E_1 \to I_1 \to I_2)$

$$\iota_2^1 = \frac{\mu_1}{\sigma + \mu_1}\frac{\sigma}{\sigma + \mu_2} + \iota_1^1 \frac{\mu_1}{\gamma_1 + \mu_1}$$

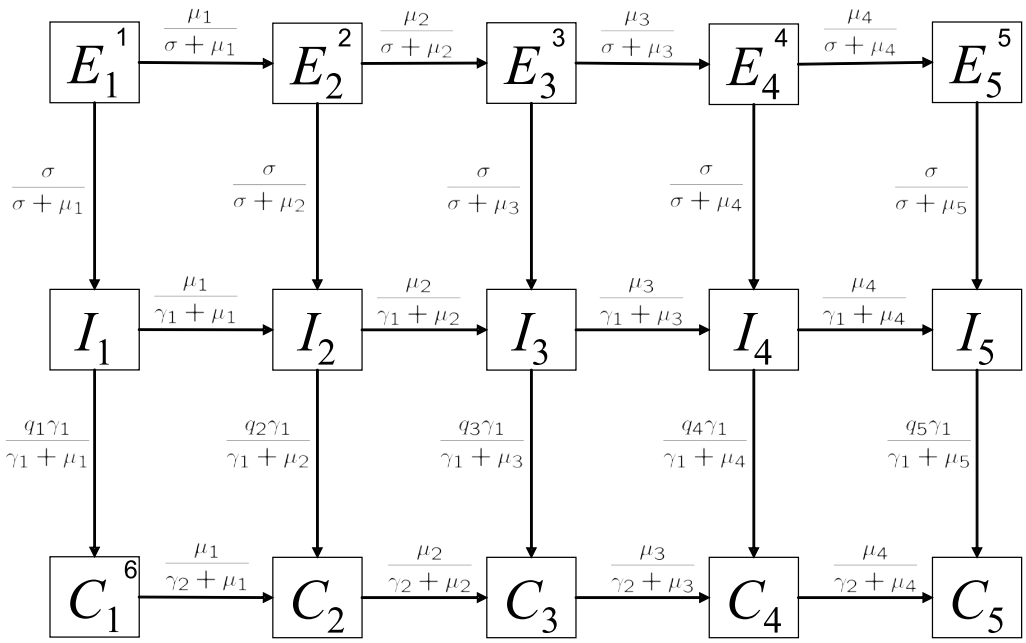


Figure 5.2: Schematic for the movement between each compartment for the five age class model. There are six ways to be infected initially: through each of the exposed compartments or by being born a carrier, denoted with superscripts.

- To become a C_2 from E_1: ($E_1 \Longrightarrow I_2 \to C_2$ and $E_1 \to C_1 \to C_2$)

$$\kappa_2^1 = \iota_2^1 \frac{q_2\gamma_1}{\gamma_1+\mu_2} + \kappa_1^1 \frac{\mu_1}{\gamma_2+\mu_1}$$

- To become an I_3 from E_1: ($E_1 \Longrightarrow E_3 \to I_3$ and $E_1 \Longrightarrow I_2 \to I_3$)

$$\iota_3^1 = \frac{\mu_1}{\sigma+\mu_1}\frac{\mu_2}{\sigma+\mu_2}\frac{\sigma}{\sigma+\mu_3} + \iota_2^1 \frac{\mu_2}{\gamma_1+\mu_2}$$

- To become a C_3 from E_1: ($E_1 \Longrightarrow I_3 \to C_3$ and $E_1 \Longrightarrow C_2 \to C_3$)

$$\kappa_3^1 = \iota_3^1 \frac{q_3\gamma_1}{\gamma_1+\mu_3} + \kappa_2^1 \frac{\mu_2}{\gamma_2+\mu_2}$$

- To become an I_4 from E_1: ($E_1 \Longrightarrow E_3 \to E_4 \to I_4$ and $E_1 \Longrightarrow I_3 \to I_4$)

$$\iota_4^1 = \frac{\mu_1}{\sigma+\mu_1}\frac{\mu_2}{\sigma+\mu_2}\frac{\mu_3}{\sigma+\mu_3}\frac{\sigma}{\sigma+\mu_4} + \iota_3^1 \frac{\mu_3}{\gamma_1+\mu_3}$$

- To become a C_4 from E_1: ($E_1 \Longrightarrow I_4 \to C_4$ and $E_1 \Longrightarrow C_3 \to C_4$)

$$\kappa_4^1 = \iota_4^1 \frac{q_4\gamma_1}{\gamma_1+\mu_4} + \kappa_3^1 \frac{\mu_3}{\gamma_2+\mu_3}$$

- To become an I_5 from E_1: ($E_1 \Longrightarrow E_4 \to E_5 \to I_5$ and $E_1 \Longrightarrow I_4 \to I_5$)

$$\iota_5^1 = \frac{\mu_1}{\sigma+\mu_1}\frac{\mu_2}{\sigma+\mu_2}\frac{\mu_3}{\sigma+\mu_3}\frac{\mu_4}{\sigma+\mu_4}\frac{\sigma}{\sigma+\mu_5} + \iota_4^1 \frac{\mu_4}{\gamma_2+\mu_4}$$

- To become a C_5 from E_1: ($E_1 \Longrightarrow I_5 \to C_5$ and $E_1 \Longrightarrow C_4 \to C_5$)

$$\kappa_5^1 = \iota_5^1 \frac{q_5\gamma_1}{\gamma_1 + \mu_5} + \kappa_4^1 \frac{\mu_4}{\gamma_2 + \mu_4}$$

Starting from E_2, the proportions that move to each of the infected and carrier compartments:

- To become an I_2 from E_2: ($E_2 \to I_2$)

$$\iota_2^2 = \frac{\sigma}{\sigma + \mu_2}$$

- To become a C_2 from E_2:($E_2 \to I_2 \to C_2$)

$$\kappa_2^2 = \iota_2^2 \frac{q_2\gamma_1}{\gamma_1 + \mu_2}$$

- To become an I_3 from E_2: ($E_2 \to E_3 \to I_3$ and $E_2 \to I_2 \to I_3$)

$$\iota_3^2 = \frac{\mu_2}{\sigma + \mu_2}\frac{\sigma}{\sigma + \mu_3} + \iota_2^2 \frac{\mu_2}{\gamma_1 + \mu_2}$$

- To become a C_3 from E_2: ($E_2 \Longrightarrow I_3 \to C_3$ and $E_2 \Longrightarrow C_2 \to C_3$)

$$\kappa_3^2 = \iota_3^2 \frac{q_3\gamma_1}{\gamma_1 + \mu_3} + \kappa_2^2 \frac{\mu_2}{\gamma_2 + \mu_2}$$

- To become an I_4 from E_2: ($E_2 \to E_3 \to E_4 \to I_4$ and $E_2 \Longrightarrow I_3 \to I_4$)

$$\iota_4^2 = \frac{\mu_2}{\sigma + \mu_2}\frac{\mu_3}{\sigma + \mu_3}\frac{\sigma}{\sigma + \mu_4} + \iota_3^2 \frac{\mu_3}{\gamma_1 + \mu_3}$$

- To become a C_4 from E_2: ($E_2 \Longrightarrow I_4 \to C_4$ and $E_2 \Longrightarrow C_3 \to C_4$)

$$\kappa_4^2 = \iota_4^2 \frac{q_4\gamma_1}{\gamma_1 + \mu_4} + \kappa_3^2 \frac{\mu_3}{\gamma_2 + \mu_3}$$

- To become an I_5 from E_2: ($E_2 \Longrightarrow E_4 \to E_5 \to I_5$ and $E_2 \Longrightarrow I_4 \to I_5$)

$$\iota_5^2 = \frac{\mu_2}{\sigma + \mu_2}\frac{\mu_3}{\sigma + \mu_3}\frac{\mu_4}{\sigma + \mu_4}\frac{\sigma}{\sigma + \mu_5} + \iota_4^2 \frac{\mu_4}{\gamma_1 + \mu_4}$$

- To become a C_5 from E_2: ($E_2 \Longrightarrow I_5 \to C_5$ and $E_2 \Longrightarrow C_4 \to C_5$)

$$\kappa_5^2 = \iota_5^2 \frac{q_5\gamma_1}{\gamma_1 + \mu_5} + \kappa_4^2 \frac{\mu_4}{\gamma_2 + \mu_4}$$

Starting from E_3, the proportions that move to each of the infected and carrier compartments:

- To become an I_3 from E_3: ($E_3 \to I_3$)

$$\iota_3^3 = \frac{\sigma}{\sigma + \mu_3}$$

- To become a C_3 from E_3: $(E_3 \to I_3 \to C_3)$

$$\kappa_3^3 = \iota_3^3 \frac{q_3\gamma_1}{\gamma_1 + \mu_3}$$

- To become an I_4 from E_3: $(E_3 \to E_4 \to I_4$ and $E_3 \to I_3 \to I_4)$

$$\iota_4^3 = \frac{\mu_3}{\sigma + \mu_3}\frac{\sigma}{\sigma + \mu_4} + \iota_3^3 \frac{\mu_3}{\gamma_1 + \mu_3}$$

- To become a C_4 from E_3: $(E3 \Longrightarrow I_4 \to C_4$ and $E_3 \Longrightarrow C_3 \to C_4)$

$$\kappa_4^3 = \iota_4^3 \frac{q_4\gamma_1}{\gamma_1 + \mu_4} + \kappa_3^3 \frac{\mu_3}{\gamma_2 + \mu_3}$$

- To become an I_5 from E_3: $(E_3 \to E_4 \to E_5 \to I_5$ and $E_3 \Longrightarrow I_4 \to I_5)$

$$\iota_5^3 = \frac{\mu_3}{\sigma + \mu_3}\frac{\mu_4}{\sigma + \mu_4}\frac{\sigma}{\sigma + \mu_5} + \iota_4^3 \frac{\mu_4}{\gamma_1 + \mu_4}$$

- To become a C_5 from E_3: $(E_3 \Longrightarrow I_5 \to C_5$ and $E_3 \Longrightarrow C_4 \to C_5)$

$$\kappa_5^3 = \iota_5^3 \frac{q_5\gamma_1}{\gamma_1 + \mu_5} + \kappa_4^3 \frac{\mu_4}{\gamma_2 + \mu_4}$$

Starting from E_4, the proportions that move to each of the infected and carrier compartments:

- To become an I_4 from E_4: $(E_4 \to I_4)$

$$\iota_4^4 = \frac{\sigma}{\sigma + \mu_4}$$

- To become a C_4 from E_4: $(E_4 \to I_4 \to C_4)$

$$\kappa_4^4 = \iota_4^4 \frac{q_4\gamma_1}{\gamma_1 + \mu_4}$$

- To become an I_5 from E_4: $(E_4 \to E_5 \to I_5$ and $E_4 \to I_4 \to I_5)$

$$\iota_5^4 = \frac{\mu_4}{\sigma + \mu_4}\frac{\sigma}{\sigma + \mu_5} + \iota_4^4 \frac{\mu_4}{\gamma_1 + \mu_4}$$

- To become a C_5 from E_4: $(E_4 \Longrightarrow I_5 \to C_5$ and $E_4 \Longrightarrow C_4 \to C_5)$

$$\kappa_5^4 = \iota_5^4 \frac{q_5\gamma_1}{\gamma_1 + \mu_5} + \kappa_4^4 \frac{\mu_4}{\gamma_2 + \mu_4}$$

Starting from E_5, the proportions that move to each of the infected and carrier compartments:

- To become an I_5 from E_5: $(E_5 \to I_5)$

$$\iota_5^5 = \frac{\sigma}{\sigma + \mu_5}$$

- To become a C_5 from E_5: $(E_5 \to I_5 \to C_5)$

$$\kappa_5^5 = \iota_5^5 \frac{q_5\gamma_1}{\gamma_1 + \mu_5}$$

Born carriers infect others immediately (from their C_1 state) or from becoming a carrier in the other age groups:

- To become a C_2 from C_1: $\frac{\mu_1}{\gamma_2+\mu_1}$
- To become a C_3 from C_1: $\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}$
- To become a C_4 from C_1: $\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3}$
- To become a C_5 from C_1:$\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3}\frac{\mu_4}{\gamma_2+\mu_4}$

Then the next generation matrix has the following entries:

$K_{1,1}$ The expected number of horizontally infected class 1 children from a single horizontally infected class 1 child:

$$\begin{aligned} K_{1,1} = \quad & \frac{\beta S_1^*}{N}\left(\iota_1^1\frac{m_{11}}{\gamma_1+\mu_1} + \iota_2^1\frac{m_{12}}{\gamma_1+\mu_2} + \iota_3^1\frac{m_{13}}{\gamma_1+\mu_3} + \iota_4^1\frac{m_{14}}{\gamma_1+\mu_4} + \iota_5^1\frac{m_{15}}{\gamma_1+\mu_5}\right) \\ & + \frac{\alpha\beta S_1^*}{N}\left(\kappa_1^1\frac{m_{11}}{\gamma_2+\mu_1} + \kappa_2^1\frac{m_{12}}{\gamma_2+\mu_2} + \kappa_3^1\frac{m_{13}}{\gamma_2+\mu_3} + \kappa_4^1\frac{m_{14}}{\gamma_2+\mu_4} + \kappa_5^1\frac{m_{15}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{1,2}$: The expected number of horizontally infected class 1 children from a single horizontally infected class 2 child:

$$\begin{aligned} K_{1,2} = \quad & \frac{\beta S_1^*}{N}\left(\iota_2^2\frac{m_{21}}{\gamma_1+\mu_2} + \iota_3^2\frac{m_{31}}{\gamma_1+\mu_3} + \iota_4^2\frac{m_{41}}{\gamma_1+\mu_4} + \iota_5^2\frac{m_{51}}{\gamma_1+\mu_5}\right) \\ & + \frac{\alpha\beta S_1^*}{N}\left(\kappa_2^2\frac{m_{21}}{\gamma_2+\mu_2} + \kappa_3^2\frac{m_{31}}{\gamma_2+\mu_3} + \kappa_4^2\frac{m_{41}}{\gamma_2+\mu_4} + \kappa_5^2\frac{m_{51}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{1,3}$: The expected number of horizontally infected class 1 children from a single horizontally infected class 3 child:

$$\begin{aligned} K_{1,3} = \quad & \frac{\beta S_1^*}{N}\left(\iota_3^3\frac{m_{31}}{\gamma_1+\mu_3} + \iota_4^3\frac{m_{41}}{\gamma_1+\mu_4} + \iota_5^3\frac{m_{51}}{\gamma_1+\mu_5}\right) \\ & + \frac{\alpha\beta S_1^*}{N}\left(\kappa_3^3\frac{m_{31}}{\gamma_2+\mu_3} + \kappa_4^3\frac{m_{41}}{\gamma_2+\mu_4} + \kappa_5^3\frac{m_{51}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{1,4}$: The expected number of horizontally infected class 1 children from a single horizontally infected class 4 adult:

$$K_{1,4} = \frac{\beta S_1^*}{N}\left(\iota_4^4\frac{m_{41}}{\gamma_1+\mu_4} + \iota_5^4\frac{m_{51}}{\gamma_1+\mu_5}\right) + \frac{\alpha\beta S_1^*}{N}\left(\kappa_4^4\frac{m_{41}}{\gamma_2+\mu_4} + \kappa_5^4\frac{m_{51}}{\gamma_2+\mu_5}\right)$$

$K_{1,5}$: The expected number of horizontally infected class 1 children from a single horizontally infected class 5 adult:

$$K_{1,5} = \frac{\beta S_1^*}{N}\left(\iota_5^5\frac{m_{51}}{\gamma_1 + \mu_5}\right) + \frac{\alpha\beta S_1^*}{N}\left(\kappa_5^5\frac{m_{51}}{\gamma_2 + \mu_5}\right)$$

$K_{1,6}$: The expected number of horizontally infected class 1 children from a single born carrier:

$$K_{1,6} = \frac{\alpha\beta S_1^*}{N}\left(\frac{m_{11}}{\gamma_2+\mu_1} + \frac{m_{12}}{\gamma_2+\mu_2}\frac{\mu_1}{\gamma_2+\mu_1} + \frac{m_{13}}{\gamma_2+\mu_3}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2} + \frac{m_{14}}{\gamma_2+\mu_4}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3} + \frac{m_{15}}{\gamma_2+\mu_5}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3}\frac{\mu_4}{\gamma_2+\mu_4}\right)$$

$K_{2,1}$: The expected number of horizontally infected class 2 children from a single horizontally infected class 1 child:

$$\begin{aligned} K_{2,1} &= \frac{\beta S_2^*}{N}\left(\iota_1^1\frac{m_{21}}{\gamma_1+\mu_1} + \iota_2^1\frac{m_{22}}{\gamma_1+\mu_2} + \iota_3^1\frac{m_{23}}{\gamma_1+\mu_3} + \iota_4^1\frac{m_{24}}{\gamma_1+\mu_4} + \iota_5^1\frac{m_{25}}{\gamma_1+\mu_5}\right) \\ &\quad + \frac{\alpha\beta S_2^*}{N}\left(\kappa_1^1\frac{m_{21}}{\gamma_2+\mu_1} + \kappa_2^1\frac{m_{22}}{\gamma_2+\mu_2} + \kappa_3^1\frac{m_{23}}{\gamma_2+\mu_3} + \kappa_4^1\frac{m_{24}}{\gamma_2+\mu_4} + \kappa_5^1\frac{m_{25}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{2,2}$: The expected number of horizontally infected class 2 children from a single horizontally infected class 2 child:

$$\begin{aligned} K_{2,2} &= \frac{\beta S_2^*}{N}\left(\iota_2^2\frac{m_{22}}{\gamma_1+\mu_2} + \iota_3^2\frac{m_{23}}{\gamma_1+\mu_3} + \iota_4^2\frac{m_{24}}{\gamma_1+\mu_4} + \iota_5^2\frac{m_{25}}{\gamma_1+\mu_5}\right) \\ &\quad + \frac{\alpha\beta S_2^*}{N}\left(\kappa_2^2\frac{m_{22}}{\gamma_2+\mu_2} + \kappa_3^2\frac{m_{23}}{\gamma_2+\mu_3} + \kappa_4^2\frac{m_{24}}{\gamma_2+\mu_4} + \kappa_5^2\frac{m_{25}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{2,3}$: The expected number of horizontally infected class 2 children from a single horizontally infected class 3 child:

$$\begin{aligned} K_{2,3} &= \frac{\beta S_2^*}{N}\left(\iota_3^3\frac{m_{32}}{\gamma_1+\mu_3} + \iota_4^3\frac{m_{42}}{\gamma_1+\mu_4} + \iota_5^3\frac{m_{52}}{\gamma_1+\mu_5}\right) \\ &\quad + \frac{\alpha\beta S_2^*}{N}\left(\kappa_3^3\frac{m_{32}}{\gamma_1+\mu_3} + \kappa_4^3\frac{m_{42}}{\gamma_1+\mu_4} + \kappa_5^3\frac{m_{52}}{\gamma_1+\mu_5}\right) \end{aligned}$$

$K_{2,4}$: The expected number of horizontally infected class 2 children from a single horizontally infected class 4 adult:

$$K_{2,4} = \frac{\beta S_2^*}{N}\left(\iota_4^4\frac{m_{42}}{\gamma_1+\mu_4} + \iota_5^4\frac{m_{52}}{\gamma_1+\mu_5}\right) + \frac{\alpha\beta S_2^*}{N}\left(\kappa_4^4\frac{m_{42}}{\gamma_1+\mu_4} + \kappa_5^4\frac{m_{52}}{\gamma_1+\mu_5}\right)$$

$K_{2,5}$: The number expected of horizontally infected class 2 children from a sinlge horizontally infected class 5 adult:

$$K_{2,5} = \frac{\beta S_2^*}{N}\iota_5^5\frac{m_{52}}{\gamma_1+\mu_5} + \frac{\alpha\beta S_2^*}{N}\kappa_5^5\frac{m_{52}}{\gamma_2+\mu_5}$$

$K_{2,6}$: The expected number of horizontally infected class 2 children from a single born carrier:

$$K_{2,6} = \frac{\alpha\beta S_2^*}{N}\left(\frac{m_{21}}{\gamma_2+\mu_1} + \frac{m_{22}}{\gamma_2+\mu_2}\frac{\mu_1}{\gamma_2+\mu_1} + \frac{m_{23}}{\gamma_2+\mu_3}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2} + \frac{m_{24}}{\gamma_2+\mu_4}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3} + \frac{m_{25}}{\gamma_2+\mu_5}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3}\frac{\mu_4}{\gamma_2+\mu_4}\right)$$

$K_{3,1}$: The expected number of horizontally infected class 3 children from a single horizontally infected class 1 child:

$$K_{3,1} = \frac{\beta S_3^*}{N}\left(\iota_1^1\frac{m_{13}}{\gamma_1+\mu_1} + \iota_2^1\frac{m_{23}}{\gamma_1+\mu_2} + \iota_3^1\frac{m_{33}}{\gamma_1+\mu_3} + \iota_4^1\frac{m_{43}}{\gamma_1+\mu_4} + \iota_5^1\frac{m_{53}}{\gamma_1+\mu_5}\right) + \frac{\alpha\beta S_3^*}{N}\left(\kappa_1^1\frac{m_{13}}{\gamma_2+\mu_1} + \kappa_2^1\frac{m_{23}}{\gamma_2+\mu_2} + \kappa_3^1\frac{m_{33}}{\gamma_2+\mu_3} + \kappa_4^1\frac{m_{43}}{\gamma_2+\mu_4} + \kappa_5^1\frac{m_{53}}{\gamma_2+\mu_5}\right)$$

$K_{3,2}$: The expected number of horizontally infected class 3 children from a single horizontally infected class 2 child:

$$K_{3,2} = \frac{\beta S_3^*}{N}\left(\iota_2^2\frac{m_{23}}{\gamma_1+\mu_2} + \iota_3^2\frac{m_{33}}{\gamma_1+\mu_3} + \iota_4^2\frac{m_{34}}{\gamma_1+\mu_4} + \iota_5^2\frac{m_{35}}{\gamma_1+\mu_5}\right) + \frac{\alpha\beta S_3^*}{N}\left(\kappa_2^2\frac{m_{23}}{\gamma_2+\mu_2} + \kappa_3^2\frac{m_{33}}{\gamma_2+\mu_3} + \kappa_4^2\frac{m_{34}}{\gamma_2+\mu_4} + \kappa_5^2\frac{m_{35}}{\gamma_2+\mu_5}\right)$$

$K_{3,3}$: The expected number of horizontally infected class 3 children from a single horizontally infected class 3 child:

$$K_{3,3} = \frac{\beta S_3^*}{N}\left(\iota_3^3\frac{m_{33}}{\gamma_1+\mu_3} + \iota_4^3\frac{m_{34}}{\gamma_1+\mu_4} + \iota_5^3\frac{m_{35}}{\gamma_1+\mu_5}\right) + \frac{\alpha\beta S_3^*}{N}\left(\kappa_3^3\frac{m_{33}}{\gamma_2+\mu_3} + \kappa_4^3\frac{m_{34}}{\gamma_2+\mu_4} + \kappa_5^3\frac{m_{35}}{\gamma_2+\mu_5}\right)$$

$K_{3,4}$: The expected number of horizontally infected class 3 children from a single horizontally infected class 4 adult:

$$K_{3,4} = \frac{\beta S_3^*}{N}\left(\iota_4^4\frac{m_{43}}{\gamma_1+\mu_4} + \iota_5^4\frac{m_{53}}{\gamma_1+\mu_5}\right) + \frac{\alpha\beta S_3^*}{N}\left(\kappa_4^4\frac{m_{43}}{\gamma_2+\mu_4} + \kappa_5^4\frac{m_{53}}{\gamma_2+\mu_5}\right)$$

$K_{3,5}$: The expected number of horizontally infected class 3 children from a single horizontally infected class 5 adult:

$$K_{3,5} = \frac{\beta S_3^*}{N}\iota_5^5\frac{m_{35}}{\gamma_1+\mu_5} + \frac{\alpha\beta S_3^*}{N}\kappa_5^5\frac{m_{35}}{\gamma_2+\mu_5}$$

$K_{3,6}$: The expected number of horizontally infected class 3 children from a single born carrier:

$$K_{3,6} = \frac{\alpha\beta S_3^*}{N}\left(\frac{m_{13}}{\gamma_2+\mu_1} + \frac{m_{23}}{\gamma_2+\mu_2}\frac{\mu_1}{\gamma_2+\mu_1} + \frac{m_{33}}{\gamma_2+\mu_3}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2} + \frac{m_{43}}{\gamma_2+\mu_4}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3} + \frac{m_{53}}{\gamma_2+\mu_5}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3}\frac{\mu_4}{\gamma_2+\mu_4}\right)$$

$K_{4,1}$: The expected number of horizontally infected class 4 adults from a single horizontally infected class 1 child:

$$\begin{aligned} K_{4,1} &= \frac{\beta S_4^*}{N}\left(\iota_1^1\frac{m_{41}}{\gamma_1+\mu_1} + \iota_2^1\frac{m_{42}}{\gamma_1+\mu_2} + \iota_3^1\frac{m_{43}}{\gamma_1+\mu_3} + \iota_4^1\frac{m_{44}}{\gamma_1+\mu_4} + \iota_5^1\frac{m_{45}}{\gamma_1+\mu_5}\right) \\ &+ \frac{\alpha\beta S_4^*}{N}\left(\kappa_1^1\frac{m_{41}}{\gamma_2+\mu_1} + \kappa_2^1\frac{m_{42}}{\gamma_2+\mu_2} + \kappa_3^1\frac{m_{43}}{\gamma_2+\mu_3} + \kappa_4^1\frac{m_{44}}{\gamma_2+\mu_4} + \kappa_5^1\frac{m_{45}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{4,2}$: The expected number of horizontally infected class 4 adults from a single horizontally infected class 2 child:

$$\begin{aligned} K_{4,2} &= \frac{\beta S_4^*}{N}\left(\iota_2^2\frac{m_{42}}{\gamma_1+\mu_2} + \iota_3^2\frac{m_{43}}{\gamma_1+\mu_3} + \iota_4^2\frac{m_{44}}{\gamma_1+\mu_4} + \iota_5^2\frac{m_{45}}{\gamma_1+\mu_5}\right) \\ &+ \frac{\alpha\beta S_4^*}{N}\left(\kappa_2^2\frac{m_{42}}{\gamma_2+\mu_2} + \kappa_3^2\frac{m_{43}}{\gamma_2+\mu_3} + \kappa_4^2\frac{m_{44}}{\gamma_2+\mu_4} + \kappa_5^2\frac{m_{45}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{4,3}$: The expected number of horizontally infected class 4 adults from a single horizontally infected class 3 child:

$$\begin{aligned} K_{4,3} &= \frac{\beta S_4^*}{N}\left(\iota_3^3\frac{m_{43}}{\gamma_1+\mu_3} + \iota_4^3\frac{m_{44}}{\gamma_1+\mu_4} + \iota_5^3\frac{m_{45}}{\gamma_1+\mu_5}\right) \\ &+ \frac{\alpha\beta S_4^*}{N}\left(\kappa_3^3\frac{m_{43}}{\gamma_2+\mu_3} + \kappa_4^3\frac{m_{44}}{\gamma_2+\mu_4} + \kappa_5^3\frac{m_{45}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{4,4}$: The expected number of horizontally infected class 4 adults from a single horizontally infected class 4 adult:

$$K_{4,4} = \frac{\beta S_4^*}{N}\left(\iota_4^4\frac{m_{44}}{\gamma_1+\mu_4} + \iota_5^4\frac{m_{45}}{\gamma_1+\mu_5}\right) + \frac{\alpha\beta S_4^*}{N}\left(\kappa_4^4\frac{m_{44}}{\gamma_2+\mu_4} + \kappa_5^4\frac{m_{45}}{\gamma_2+\mu_5}\right)$$

$K_{4,5}$: The expected number of horizontally infected class 4 adults from a single horizontally infected class 5 adult:

$$K_{4,5} = \frac{\beta S_4^*}{N}\iota_5^5\frac{m_{45}}{\gamma_1+\mu_5} + \frac{\alpha\beta S_4^*}{N}\kappa_5^5\frac{m_{45}}{\gamma_2+\mu_5}$$

$K_{4,6}$: The expected number of horizontally infected class 4 adults from a born carrier:

$$K_{4,6} = \frac{\alpha\beta S_4^*}{N}\left(\frac{m_{14}}{\gamma_2+\mu_1} + \frac{m_{24}}{\gamma_2+\mu_2}\frac{\mu_1}{\gamma_2+\mu_1} + \frac{m_{34}}{\gamma_2+\mu_3}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2} + \frac{m_{44}}{\gamma_2+\mu_4}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3} + \frac{m_{54}}{\gamma_2+\mu_5}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3}\frac{\mu_4}{\gamma_2+\mu_4}\right)$$

$K_{5,1}$: The expected number of horizontally infected class 5 adults from a single horizontally infected class 1 child:

$$\begin{aligned} K_{5,1} &= \frac{\beta S_5^*}{N}\left(\iota_1^1\frac{m_{51}}{\gamma_1+\mu_1}+\iota_2^1\frac{m_{52}}{\gamma_1+\mu_2}+\iota_3^1\frac{m_{53}}{\gamma_1+\mu_3}+\iota_4^1\frac{m_{54}}{\gamma_1+\mu_4}+\iota_5^1\frac{m_{55}}{\gamma_1+\mu_5}\right) \\ &\quad +\frac{\alpha\beta S_5^*}{N}\left(\kappa_1^1\frac{m_{51}}{\gamma_2+\mu_1}+\kappa_2^1\frac{m_{52}}{\gamma_2+\mu_2}+\kappa_3^1\frac{m_{53}}{\gamma_2+\mu_3}+\kappa_4^1\frac{m_{54}}{\gamma_2+\mu_4}+\kappa_5^1\frac{m_{55}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{5,2}$: The expected number of horizontally infected class 5 adults from a single horizontally infected class 2 child:

$$\begin{aligned} K_{5,2} &= \frac{\beta S_5^*}{N}\left(\iota_2^2\frac{m_{52}}{\gamma_1+\mu_2}+\iota_3^2\frac{m_{53}}{\gamma_1+\mu_3}+\iota_4^2\frac{m_{54}}{\gamma_1+\mu_4}+\iota_5^2\frac{m_{55}}{\gamma_1+\mu_5}\right) \\ &\quad +\frac{\alpha\beta S_5^*}{N}\left(\kappa_2^2\frac{m_{52}}{\gamma_2+\mu_2}+\kappa_3^2\frac{m_{53}}{\gamma_2+\mu_3}+\kappa_4^2\frac{m_{54}}{\gamma_2+\mu_4}+\kappa_5^2\frac{m_{55}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{5,3}$: The expected number of horizontally infected class 5 adults from a single horizontally infected class 3 child:

$$\begin{aligned} K_{5,3} &= \frac{\beta S_5^*}{N}\left(\iota_3^3\frac{m_{35}}{\gamma_1+\mu_3}+\iota_4^3\frac{m_{45}}{\gamma_1+\mu_4}+\iota_5^3\frac{m_{55}}{\gamma_1+\mu_5}\right) \\ &\quad +\frac{\alpha\beta S_5^*}{N}\left(\kappa_3^3\frac{m_{35}}{\gamma_2+\mu_3}+\kappa_4^3\frac{m_{45}}{\gamma_2+\mu_4}+\kappa_5^3\frac{m_{55}}{\gamma_2+\mu_5}\right) \end{aligned}$$

$K_{5,4}$: The expected number of horizontally infected class 5 adults from a single horizontally infected class 4 adult:

$$K_{5,4} = \frac{\beta S_5^*}{N}\left(\iota_4^4\frac{m_{45}}{\gamma_1+\mu_4}+\iota_5^4\frac{m_{55}}{\gamma_1+\mu_5}\right)+\frac{\alpha\beta S_5^*}{N}\left(\kappa_4^4\frac{m_{45}}{\gamma_2+\mu_4}+\kappa_5^4\frac{m_{55}}{\gamma_2+\mu_5}\right)$$

$K_{5,5}$: The expected number of horizontally infected class 5 adults from a single horizontally infected class 5 adult:

$$K_{5,5} = \frac{\beta S_5^*}{N}\iota_5^5\frac{m_{55}}{\gamma_1+\mu_5}+\frac{\alpha\beta S_5^*}{N}\kappa_5^5\frac{m_{55}}{\gamma_2+\mu_5}$$

$K_{5,6}$: The expected number of horizontally infected class 5 adults from a single born carrier:

$$\begin{aligned} K_{5,6} = \frac{\alpha\beta S_5^*}{N}\Bigg(&\frac{m_{15}}{\gamma_2+\mu_1}+\frac{m_{25}}{\gamma_2+\mu_2}\frac{\mu_1}{\gamma_2+\mu_1}+\frac{m_{35}}{\gamma_2+\mu_3}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2} \\ &+\frac{m_{45}}{\gamma_2+\mu_4}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3} \\ &+\frac{m_{55}}{\gamma_2+\mu_5}\frac{\mu_1}{\gamma_2+\mu_1}\frac{\mu_2}{\gamma_2+\mu_2}\frac{\mu_3}{\gamma_2+\mu_3}\frac{\mu_4}{\gamma_2+\mu_4}\Bigg) \end{aligned}$$

$K_{6,1}$: The expected number of born carriers from a single horizontally infected class 1 child:

$$K_{6,1} = \kappa_4^1\frac{\nu B}{N_4(\gamma_2+\mu_4)}$$

$K_{6,2}$: The expected number of born carriers from a single horizontally infected class 2 child:

$$K_{6,2} = \kappa_4^2 \frac{\nu B}{N_4(\gamma_2 + \mu_4)}$$

$K_{6,3}$: The expected number of born carriers from a single horizontally infected class 3 child:

$$K_{6,3} = \kappa_4^3 \frac{\nu B}{N_4(\gamma_2 + \mu_4)}$$

$K_{6,4}$: The expected number of born carriers from a single horizontally infected class 4 adult:

$$K_{6,4} = \kappa_4^4 \frac{\nu B}{N_4(\gamma_2 + \mu_4)}$$

$K_{6,5}$: The expected number of born carriers from a single horizontally infected class 5 adult:

$$K_{6,5} = 0$$

$K_{6,6}$: The expected number of born carriers from a single born carrier:

$$K_{6,6} = \frac{\nu B}{N_4(\gamma_2 + \mu_4)} \frac{\mu_1}{\gamma_2 + \mu_1} \frac{\mu_2}{\gamma_2 + \mu_2} \frac{\mu_3}{\gamma_2 + \mu_3}$$

To find the basic reproduction ratio we let each $S_i^* = N_i = B/\mu_i$ (as the population is fully susceptible to infection) in K, and then find largest eigenvalue of K. To calculate the steady state of the system, Equations (5.1)–(5.5) were solved numerically until a steady state was found (the solutions to the equations were calculated until 2500 years to ensure a steady state had been reached). We can then obtain a bifurcation diagram, Figure 5.3, by plotting the steady state of our equations for various values of R_0.

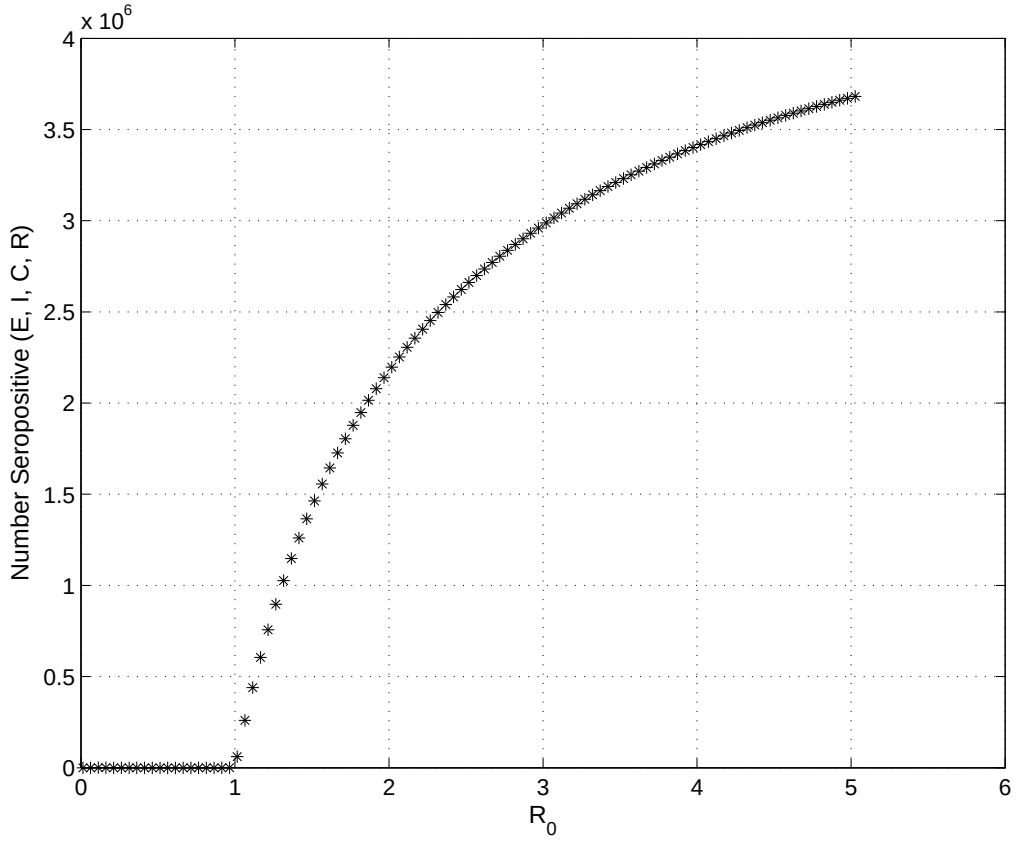


Figure 5.3: Bifurcation diagram for the five age classes model - the number of people who have been infected (the exposed, carrier, infected and recovered classes) plotted against the basic reproduction ratio. The zero steady state becomes unstable when R_0 increases past one, and the second branch is stable. This was generated numerically using the parameters given in Table 5.1, and the epidemic is run for a minimum of 2500 years, or until the system reaches an equilibrium.

Symbol	Parameter Description	Value
σ	the rate at which exposed individuals become infective	6 per year
γ_1	the rate at which acutely infected individuals recover	4 per year
γ_2	the rate at which carrier individuals recover	0.025 per year
β	transmission coefficient	2.2
α	infectiousness of carriers relative to acutely infected individuals	0.5
μ_1	death rate of age class 1	12/15 per year
μ_2	death rate of age class 2	4/19 per year
μ_3	death rate of age class 3	1/10 per year
μ_4	death rate of age class 4	1/29 per year
μ_5	death rate of age class 5	1/25 per year
B	Birth rate	64460 births
q_1	the proportion of age class 1 who become carriers	0.2551
q_2	the proportion of age class 2 who become carriers	0.1285
q_3	the proportion of age class 3 who become carriers	0.0651
q_4	the proportion of age class 4 who become carriers	0.0382
q_5	the proportion of age class 5 who become carriers	0.0073

Table 5.1: The parameters and variables used 5 age class model for Hepatitis B infection in New Zealand.

Comparing the model to known data

The data available on the recorded number of cases of Hepatitis B in New Zealand can be split into two eras: data recorded between 1971 (when records began) and 1984; and after 1984. Prior to 1984 the number of notifications recorded included not only notifications of the acute infection, but also included notifications of the chronic carrier state. After 1984, only the acute cases were recorded. Asymptomatic infection occurs in approximately 60% of infections (New Zealand Ministry of Health (2006)), whereas acute hepatitis is rare, with only 6% of children and 33% of adults presenting as acute infections, so we should bear in mind that not all cases of infection would have been recorded.

To compare our model with this data we need to calculate the incidence of infection (i_j) and carriage (c_j) each year for each age group $j \in \{1..5\}$. This is calculated from the equations below:

$$\begin{aligned} i_1 &= \sigma E_1 & c_1 &= \omega\nu\tfrac{C_4}{N_4}B + q_1\gamma_1 I_1 \\ i_2 &= \sigma E_2 & c_2 &= q_2\gamma_1 I_2 \\ i_3 &= \sigma E_3 & c_3 &= q_3\gamma_1 I_3 \\ i_4 &= \sigma E_4 & c_4 &= q_4\gamma_1 I_4 \\ i_5 &= \sigma E_5 & c_5 &= q_5\gamma_1 I_5 \end{aligned}$$

Vaccination against Hepatitis B was introduced in New Zealand in 1985, when newborn babies of carrier mothers were vaccinated (the parameter ν captures the effect of this in our model). In 1987 this vaccination was extended to babies that were also born in areas deemed to be "high risk". From 1988, the vaccination was given in four doses: at birth, six weeks, three months and 15 months of age, and in 1988 there was also a catch up campaign for pre-schoolers. The vaccination at birth was removed from the vaccination schedule in 1989 as a different vaccine was used, and it was only newborns to carrier mothers who received the vaccination at birth. From early 1990, a free immunisation was offered to all children under the age of 16.

The schedule was last changed in 1996, with the third dose being brought forward from 15 months to five months of age, with a vaccination at birth offered to children born from mothers carrying the virus.

The modelled incidence of acute infection without vaccination is shown in Figure 5.4. The epidemic was seeded with one carrier and one acutely infected person in age group four in 1900, with a basic reproduction ratio of 1.54. The parameter values were taken from Medley *et al.* (2001) (apart from the birth and death rates). Our model has not produced a very good fit to the data, as we have a slow rate of increase in the incidence of infection.

To include the effects of vaccination in our model we altered the values of ω, ν and P_i:

$$\nu = \begin{cases} 0.11 & \text{if } t < 1985 \\ 0.01 & \text{if } t \geq 1985 \end{cases} \tag{5.9}$$

$$\omega = \begin{cases} 1 & \text{if } t < 1987 \\ 0.6 & \text{if } 1987 \leq t < 1988 \\ 0.4 & \text{if } 1988 \leq t < 1989 \\ 1 & \text{if } t \geq 1989 \end{cases} \tag{5.10}$$

$$P_1 = \begin{cases} 0 & \text{if } t < 1988 \\ 0.8 & \text{if } 1988 \leq t < 1996 \\ 0.99 & \text{it } t \geq 1996 \end{cases} \tag{5.11}$$

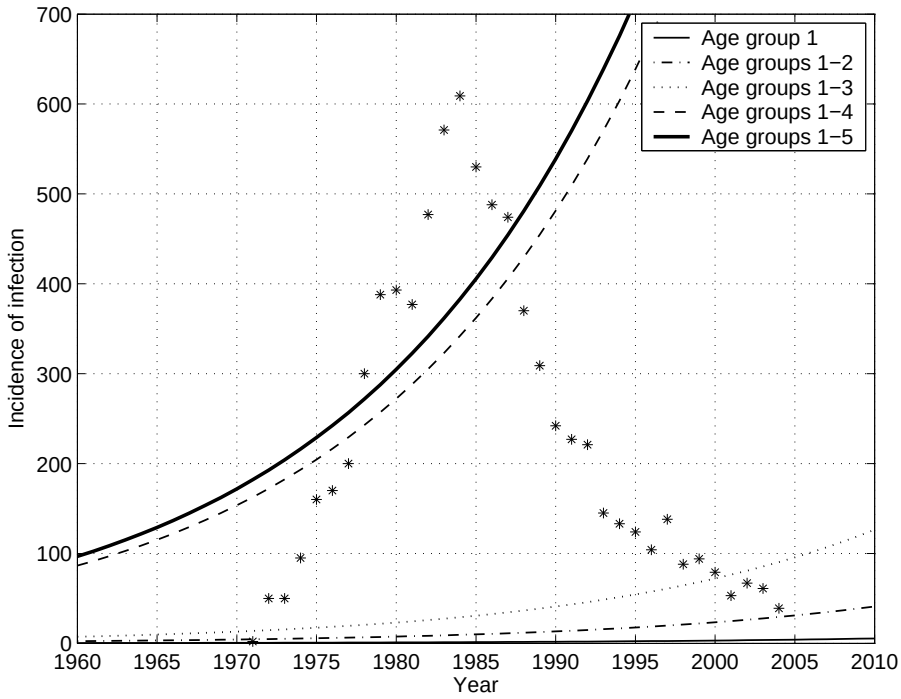


Figure 5.4: The incidence of infection for the five age group model, using the same parameters given in Medley *et al.* (2001). The stars are the recorded incidence of infection and chronic carriers prior to 1984, then only the incidence of acute infection after 1984. Vaccination against Hepatitis B was started in 1985 which also contributed to the decrease in the recorded incidence of infection. $R_0 = 1.54$.

$$P_2 = \begin{cases} 0 & \text{if } t < 1988 \\ 0.9 & \text{if } t \geq 1988 \end{cases} \tag{5.12}$$

$$P_3 = \begin{cases} 0 & \text{if } t < 1990 \\ 0.2 & \text{if } t \geq 1990 \end{cases} \tag{5.13}$$

These rates incorporate both the coverage of vaccination and the efficacy of the vaccine. The incidence of infection once the effect of vaccination is included is shown in Figure 5.5. We can see that vaccination does decrease the incidence of infection in our population, but our incidence does not decrease as quickly as the observed rate. To alter the speed at which the epidemic progresses, the parameters for each age group need to be varied, as we show in the next section. For this model the average amount of time spent in each compartment is given in Table 5.2.

	Compartment			
Age Group	E	I	C	R
One	7.6 weeks	10.8 weeks	1.21 years	1.25 years
Two	8.3 weeks	12.35 weeks	4.25 years	4.75 years
Three	8.5 weeks	12.68 weeks	8 years	10 years
Four	8.6 weeks	12.9 weeks	16.8 years	29 years
Five	8.6 weeks	12.9 weeks	15.4 years	25 years

Table 5.2: The average time spent in each of the exposed, acutely infected, carrier and removed compartments for the five age group model with the same parameters as Medley *et al.* (2001).

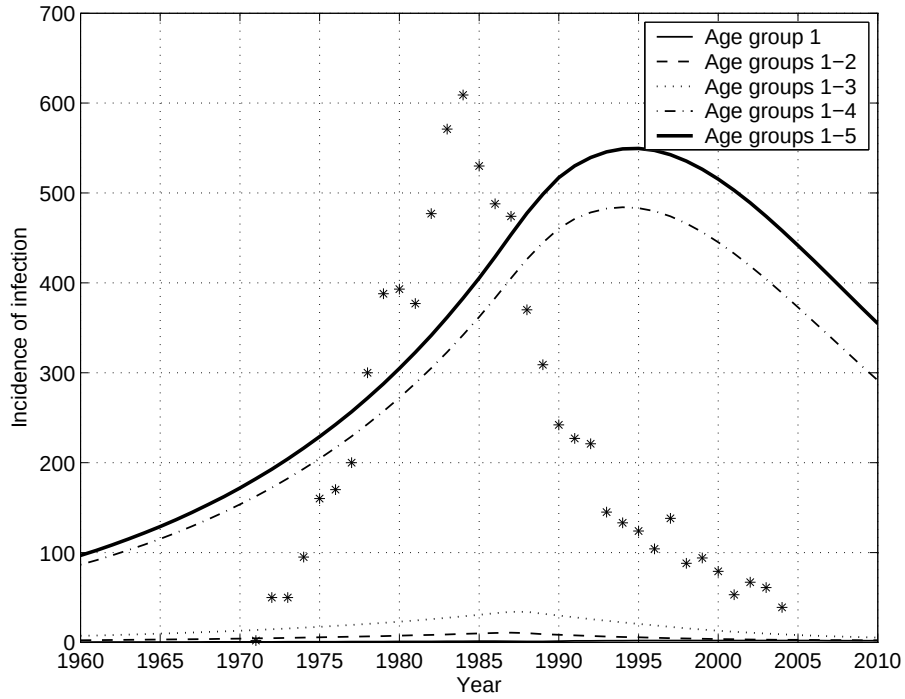


Figure 5.5: The incidence of infection for our five age group model with vaccination included. The stars represent the recorded incidence of infection (and include chronic carriers prior to 1984).

5.3 Five age group model with age dependent parameters

In the model given in section 5.2, the average time spent in each compartment varied with age, due to the rates of movement between compartments being the same for each age group, even though they all had different death rates. Using a similar type of system as previously, we now let the rate at which people who become acutely infected, and the rate at which acutely infected and carriers recover depend on age. The latency period between being infected and becoming acutely infected (or infectious) is between 4–10 weeks, so we set each of our σ_j values to give the average time in each E_j compartment as 0.07. Similarly, we know that acute infection (or the period that a person remains infectious) is between 3–12 weeks, so we set our γ_j parameters from the I_j compartments, to give an average time in each I_j compartment as 0.12. Approximately 1–6% of carriers will naturally clear infection, so our γ_j values in each C_j compartment are set to 0.03 – for all age classes. Thus our system is now:

$$\text{group 1 (0–1.25 years old)} \begin{cases} \frac{dS_1}{dt} = \left(\omega_0 - \omega_1\nu\frac{C_4}{N_4}\right)B(t) - (\lambda_1 + \mu_1)S_1 \\ \frac{dE_1}{dt} = \lambda_1 S_1 - (\sigma_1 + \mu_1)E_1 \\ \frac{dI_1}{dt} = \sigma_1 E_1 - (\gamma_1 + \mu_1)I_1 \\ \frac{dC_1}{dt} = \omega_1\nu\frac{C_4}{N_4}B(t) + q_1\gamma_1 I_1 - (\gamma_2 + \mu_1)C_1 \\ \frac{dR_1}{dt} = (1-\omega_0)B + (1-q_1)\gamma_1 I_1 + \gamma_2 C_1 - \mu_1 R_1 \end{cases} \tag{5.14}$$

$$\text{group 2 (1.25–6 years old)} \begin{cases} \frac{dS_2}{dt} = (1 - P_1(t))\mu_1 S_1 - (\lambda_2 + \mu_2)S_2 \\ \frac{dE_2}{dt} = \mu_1 E_1 + \lambda_2 S_2 - (\sigma_2 + \mu_2)E_2 \\ \frac{dI_2}{dt} = \mu_1 I_1 + \sigma_2 E_2 - (\gamma_3 + \mu_2)I_2 \\ \frac{dC_2}{dt} = \mu_1 C_1 + q_2\gamma_3 I_2 - (\gamma_4 + \mu_2)C_2 \\ \frac{dR_2}{dt} = \mu_1 R_1 + P_1(t)\mu_1 S_1 + (1-q_2)\gamma_3 I_2 + \gamma_4 C_2 - \mu_2 R_2 \end{cases} \tag{5.15}$$

$$\text{group 3 (6–16 years old)} \begin{cases} \frac{dS_3}{dt} = (1 - P_2(t))\mu_2 S_2 - (\lambda_3 + \mu_3)S_3 \\ \frac{dE_3}{dt} = \mu_2 E_2 + \lambda_3 S_3 - (\sigma_3 + \mu_3)E_3 \\ \frac{dI_3}{dt} = \mu_2 I_2 + \sigma_3 E_3 - (\gamma_5 + \mu_3)I_3 \\ \frac{dC_3}{dt} = \mu_2 C_2 + q_3\gamma_5 I_3 - (\gamma_6 + \mu_3)C_3 \\ \frac{dR_3}{dt} = \mu_2 R_2 + P_2(t)\mu_2 S_2 + (1-q_3)\gamma_5 I_3 + \gamma_6 C_3 - \mu_3 R_3 \end{cases} \tag{5.16}$$

$$\text{group 4 (16–45 years old)} \begin{cases} \frac{dS_4}{dt} = (1 - P_3(t))\mu_3 S_3 - (\lambda_4 + \mu_4)S_4 \\ \frac{dE_4}{dt} = \mu_3 E_3 + \lambda_4 S_4 - (\sigma_4 + \mu_4)E_4 \\ \frac{dI_4}{dt} = \mu_3 I_3 + \sigma_4 E_4 - (\gamma_7 + \mu_4)I_4 \\ \frac{dC_4}{dt} = \mu_3 C_3 + q_4\gamma_7 I_4 - (\gamma_8 + \mu_4)C_4 \\ \frac{dR_4}{dt} = P_3(t)\mu_3 S_3 + \mu_3 R_3 + (1 - q_4)\gamma_7 I_4 + \gamma_8 C_4 - \mu_4 R_4 \end{cases} \tag{5.17}$$

$$\text{group 5 (45–70 years old)} \begin{cases} \frac{dS_5}{dt} = \mu_4 S_4 - (\lambda_5 + \mu_5)S_5 \\ \frac{dE_5}{dt} = \mu_4 E_4 + \lambda_5 S_5 - (\sigma_5 + \mu_5)E_5 \\ \frac{dI_5}{dt} = \mu_4 I_4 + \sigma_5 E_5 - (\gamma_9 + \mu_5)I_5 \\ \frac{dC_5}{dt} = \mu_4 C_4 + q_5\gamma_9 I_5 - (\gamma_{10} + \mu_5)C_5 \\ \frac{dR_5}{dt} = \mu_4 R_4 + (1 - q_5)\gamma_9 I_5 + \gamma_{10} C_5 - \mu_5 R_5 \end{cases} \tag{5.18}$$

where

$$\lambda_i = \frac{\beta}{\sum_{k=1}^{5} N_k} \sum_{j=1}^{5} m_{ij}(I_j + \alpha C_j) \tag{5.19}$$

$$\frac{dN}{dt} = B(t) - \mu_5 N_5 \tag{5.20}$$

We introduce two vaccination parameters ω_0 and ω_1 for infants. This is so we will not vary the parameter ν to take into account vaccinating new borns of carrier mothers, but keep it fixed and vary ω_1 instead. The proportion of babies born to carrier mothers who are vaccinated at birth is ω_1, and the proportion of babies born to non-infected mothers who are vaccinated is ω_0. The value of ω_1 is slightly higher than the vaccination rate for all new borns, as the carrier status of a mother is probably not known in many cases.

Once infected with HBV there is an incubation period of four to ten weeks, the acute phase lasts for several weeks and chronic carriage can last for the rest of the persons life. At present, we not aware that re-infection is possible, so once a person enters the removed compartment they stay there for the rest of their life. Approximately 60% of those infected are asymptomatic, it is unlikely that these cases will be recorded so we expect our model to show a higher yearly incidence of infection than the known data. Also noting that the recorded data before 1985 included both chronic carriers and acutely infected people, then after 1985 only acutely infected people, we expect the effect of vaccination to show later in our model than in the data (vaccination was also started in 1985).

The mixing matrix was set with a weighting of 0.6 for mixing between age groups, with age group 2 have the highest activity level ($a_1 = 1$, $a_2 = 6$, $a_3 = 3$, $a_4 = 2$, and $a_5 = 1$). Using these values, we then solve our new system numerically in MATLAB, we plot only 40% of the yearly incidence of infection and include the incidence of carriage for the years before 1985, and we have included the effects of the vaccination campaign. The results of this can be seen in Figure 5.6, plotted with the known yearly incidence of infection (shown as stars). We calculated the next generation matrix in a similar manner

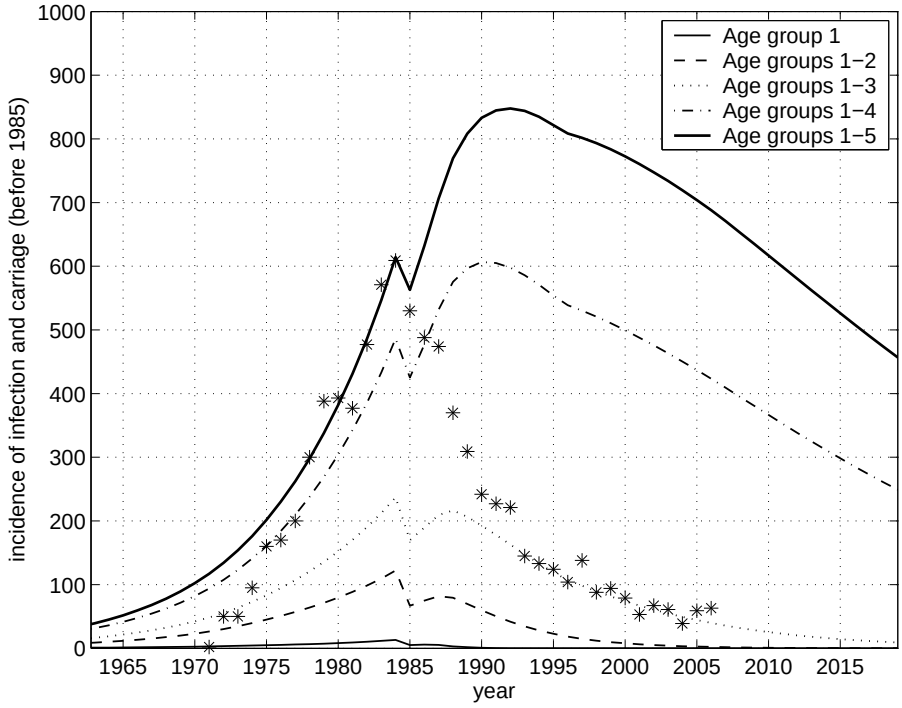
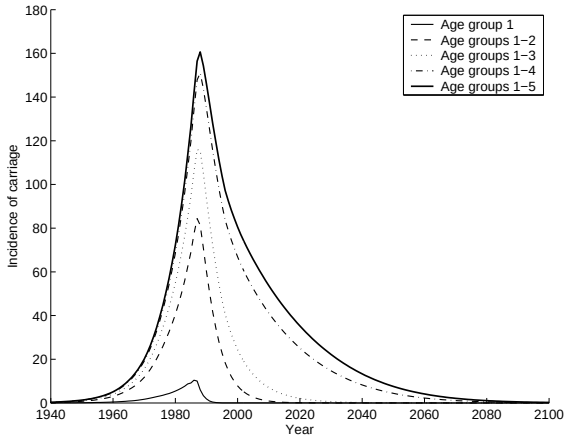


Figure 5.6: The incidence of infection (and carriage prior to 1985) shown by the stars and our model results (bottom curve is the incidence in the first age class, the second curve is the incidence in age classes 1 and 2, so on to the top curve with is the total incidence). Only 40% of the models yearly incidence of infection is plotted, and the yearly incidence of carriage is included before 1985. $R_0 = 3.2$

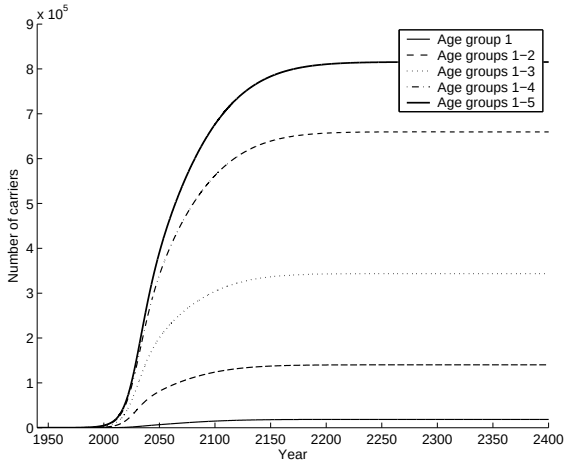
to our last model, and have a basic reproduction ratio of 3.2 for this example. We let $\alpha = 1$, and started the epidemic in 1940 with one carrier in age classes 3 and 4 and one infected in age class 4.

Even with the effect of vaccination included in our model, our results do not show the decrease that was seen in the reported incidence of infection. This is mainly due to the large reservoir of carriers that are still present in the population, as the vaccination does not affect people who are already in the carriage state. The yearly incidence of carriage decreases after the vaccination campaign was started (as shown in Figure 5.7(a)), but as carriage is often life long after infection, the total number of carriers remains very high (shown in Figure 5.7(b)).

For the previous example we let $\alpha = 1$, implying that carriers are equally as infectious as acutely infected individuals. If we let α be much smaller than one, then carriers would not have as great an impact on the spread of infection. Figure 5.6 shows a large number of cases in the adult age groups, which is not reflected in the data. This could imply that there is a further difference between the infection process in adults and children, and that adults are less likely to be infected given contact with an infectious person. We now let α be very small, and let the probability of being infected given contact with an infectious



(a)



(b)

Figure 5.7: (a) shows the cumulative incidence of carriage (with vaccination) for the five age classes, where (b) shows the cumulative number of carriers in each age class (with vaccination). Although the incidence of carriage decreases after the vaccination campaign was initiated, the total number of carriers in the population remains high. $R_0 = 3.2$

person decrease with age, thus changing our λ parameters (for $j = 1..5$):

$$\begin{aligned}
\lambda_1 &= \frac{\beta}{N}\sum_{j=1}^{5} m_{1j}(I_j + \alpha C_j) \\
\lambda_2 &= \frac{\beta}{N}\sum_{j=1}^{5} m_{2j}(I_j + \alpha C_j) \\
\lambda_3 &= \frac{0.75\beta}{N}\sum_{j=1}^{5} m_{3j}(I_j + \alpha C_j) \\
\lambda_4 &= \frac{0.35\beta}{N}\sum_{j=1}^{5} m_{4j}(I_j + \alpha C_j) \\
\lambda_5 &= \frac{0.3\beta}{N}\sum_{j=1}^{5} m_{5j}(I_j + \alpha C_j)
\end{aligned} \tag{5.21}$$

According to the New Zealand Ministry of Health (New Zealand Ministry of Health (2006)), acute hepatitis occurs rarely in infants and in approximately 6 percent of infected children. It is higher in adults, reaching approximately 33 percent. To adjust our model for this, we shall only graph 1 percent of the incidence of infection in our first age group (new borns to 15 months old), 6 percent of our second age group (15 month to 6 years old) incidence, 10 percent of our third age group (6 years to 16 years old) incidence, 30 percent of our fourth age group incidence (16 to 45 years old), and 33 percent of our fifth age group (45 to 70 years old) incidence – as these are the percentage of acute infections in each age group that we would expect to be reported. The results of this are shown in Figure 5.8. We have not included the incidence of carriage in our results this time when comparing our model to data, as it is unlikely that people newly acquiring carriage would have been reported prior to 1985. Thus we expect our model predictions to be lower than the recorded incidence before 1985.

The total yearly incidence of infection and carriage are shown in Figure 5.9, without adjusting for the percentage that present acute infection. Our model predicts a peak total incidence of just over 3200 in 1988, and a peak total incidence of carriage of 171 in 1987. We would expect the incidence of carriage to decrease soon after the introduction of vaccination, as the vaccination campaign was aimed at children who are most likely to become carriers if they are infected.

Without vaccination, our model results for the yearly incidence of infection and carriage are shown in Figure 5.10. If there were no vaccination, our model predicts that there would have been a peak total of nearly 5,000 infections (in 2035), and a peak yearly incidence of carriage of approximately 3,250 (in 2042). The introduction of vaccination caused a decrease in the incidence of carriage before a decrease in the incidence of infection, however this is reversed when there is no vaccination.

Our model gives a basic reproduction ratio of 1.5. We can look at the reproduction ratio during the course of the epidemic (R_t) and compare this to the reproduction ratio

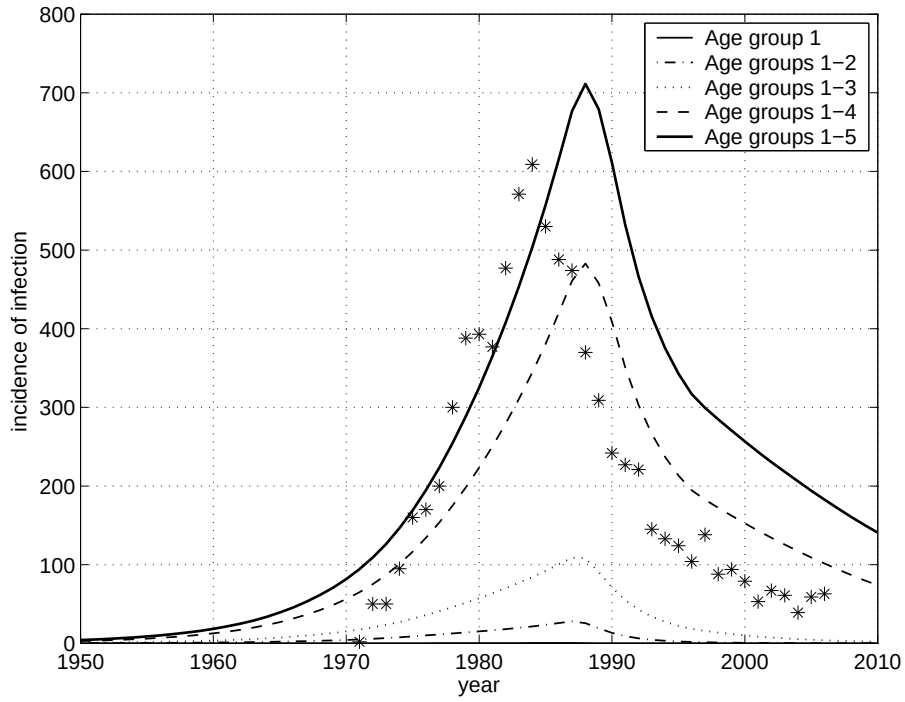
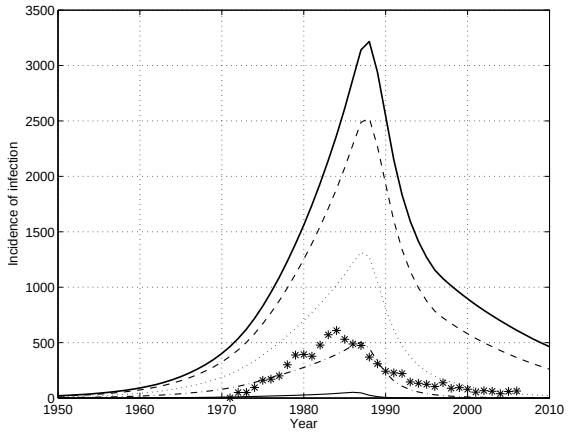


Figure 5.8: The incidence of infection (and carriage prior to 1985) shown by the stars and our model results with percentage of incidence plotted increasing with age (bottom curve is the incidence in the first age class, the second curve is the incidence in age classes 1 and 2, so on to the top curve with is the total incidence). $R_0 = 1.5$

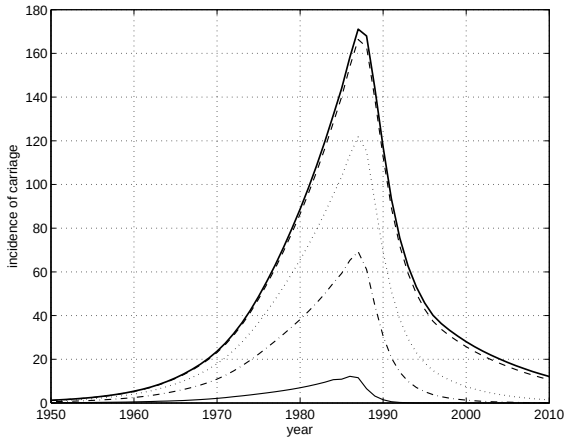
under vaccination (R_{vt}) – both of which are shown in Figure 5.11. The introduction of vaccination to babies in high risk areas caused the reproduction ratio under vaccination to suddenly decrease, the earlier introduction of vaccination to babies of carrier mothers caused only a slight decrease. As shown, without vaccination, the reproduction ratio would have eventually settled down to approximately one, which would have most likely caused sporadic outbreaks of epidemics.

We have assumed a low level of inter-age group mixing for this example, with $\epsilon = 0.25$, and the highest activity level being for our second age group – 15 month –6 years old ($a_1 = 1$, $a_2 = 1.75$, $a_3 = 1.25$, $a_4 = 1$, and $a_5 = 1$). The inter-age group mixing is assumed to be low due to the nature in which Hepatitis B is transmitted, and the highest activity levels are given to the pre-school aged children and school aged children as these age groups reported the highest number of cases.

Figure 5.12 shows the actual number of carriers present in the population at any time cumulatively for the five age groups. Gane (2005) states that there were an estimated 67,000 New Zealanders with chronic Hepatitis B (or 1.96% of the target population) – what we would include as a carrier in our model – with data taken from a screening programme that ran for three years from 1999. Gane based his estimate on the results published by Robinson *et al.* (2005), where only those aged over 15 were included in the target population. Robinson *et al.* (2005) assumed that those aged under 15 years would

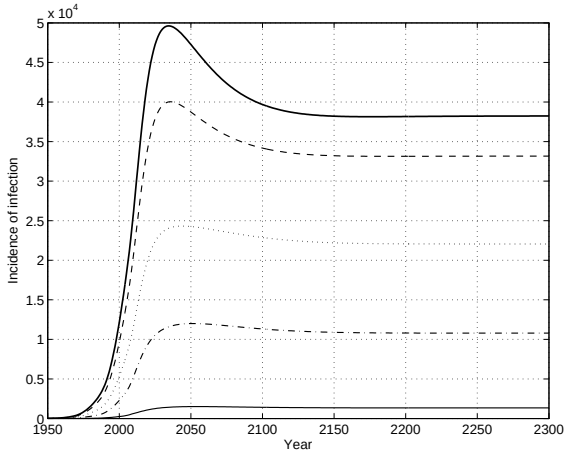


(a)

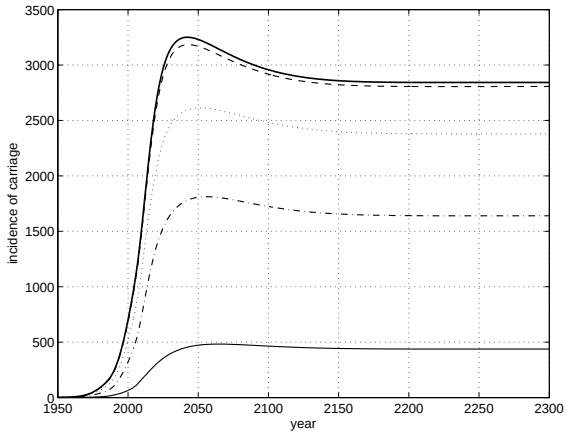


(b)

Figure 5.9: (a) shows the total incidence of infection for our four age groups (group 1 is the lowest curve, followed by group 1 and 2 (dot-dashed curve), all the way up to the total incidence (solid line)). The recorded incidence of infection is shown by the stars. (b) shows the yearly incidence of carriage for the four age groups, with the highest solid line being the total incidence of carriage.



(a)



(b)

Figure 5.10: (a) shows the incidence of infection for the cumulative four age classes if there was no vaccination campaign, and (b) shows the cumulative yearly incidence of carriage for the four age classes in the absence of vaccination.

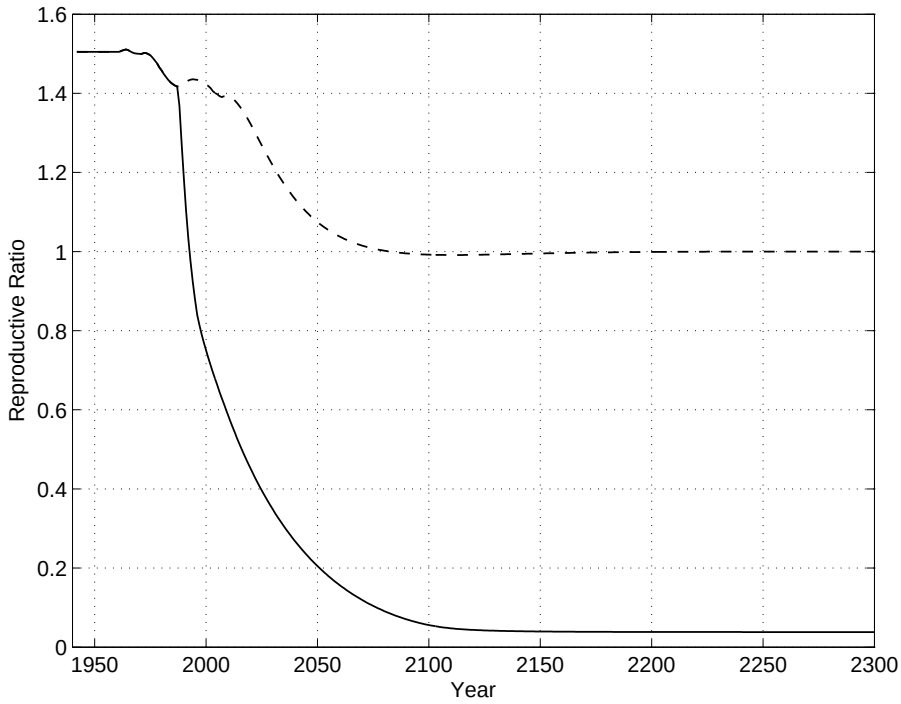


Figure 5.11: The reproduction ratios plotted over the course of the epidemic. R_{tv} (the ratio when vaccination is included) is shown as a solid line, and R_t (the ratio with no vaccination) is shown by the dashed line.

have been affected by the vaccination campaign, and hence play little role (if any) in the prevalence of carriage. Our model predicts that there were nearly 1,557 (0.04% of the total population) who were carriers in 1999, but this reduced to 1,469 (0.03% of the total population) by 2002. One reason for our figures not being the same is that we have looked at the entire population, rather than those aged over 15 years.

For our model to give a higher number of carriers (to be in line with Gane (2005)), we would have to drastically lower the percentage of acute cases for each age group and significantly increase the basic reproduction ratio. This would then make our model parameters very different from what has been published in the literature. As there are no data available on prevalence within age groups, we can assume that there is some aspect of the infection process that our model is not capturing. It is also difficult to compare our model to the known yearly incidence of infections, as the data prior to 1985 includes both acute infections and carriers – of which the carriers could have been in the carriage state for a number of years.

5.3.1 Other Vaccination Schemes

Although our model does not follow the data exactly, we can use it to predict what would have happened if the vaccination schedule had not been implemented as it was. If only babies to carrier mothers and new borns were vaccinated (assuming a near perfect

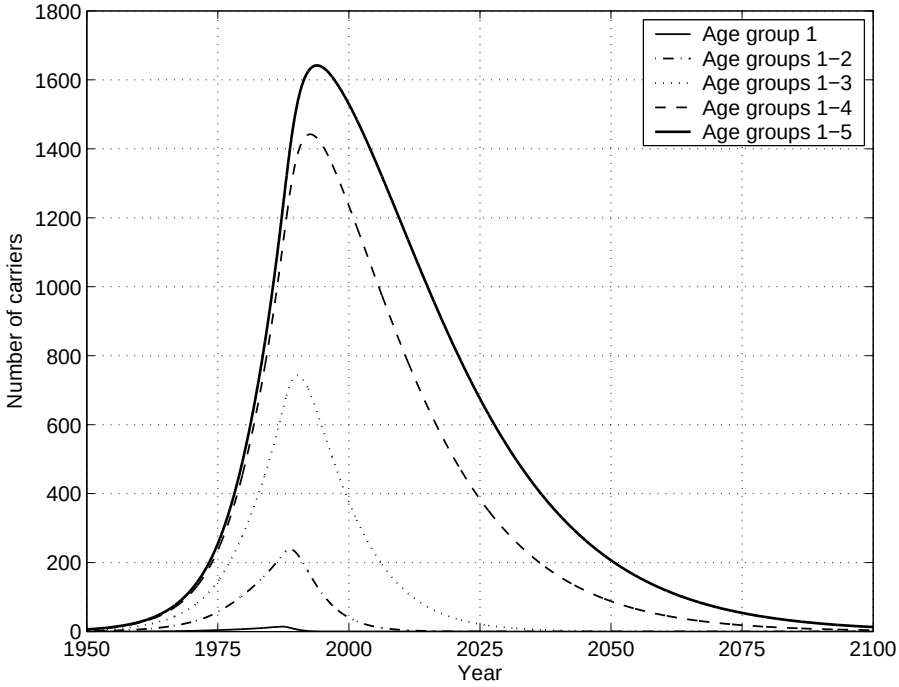


Figure 5.12: The five age class model results for the number of carriers in the population at any time.

efficiency of the vaccine and a 95% coverage), the resulting yearly incidence of infection is shown in Figure 5.13 with the corresponding model results for the full vaccination scheme. From this scheme, there would not have been a significant increase in the number of infection in children, but the number of infections in adults would have been higher, and remained high for longer. With vaccinating only babies, the reproduction ratio would have only decreased to 0.1 (after some time), as opposed to the 0.04 that the full vaccination scheme predicts.

From Figure 5.9(a) the predicted true number of acute infections was already high before the vaccination campaign was launched. What would have happened if the same vaccination campaign could have been launched five years earlier? The results of this are shown in Figure 5.14. At first glance, the results look very similar to those from the actual vaccination campaign, but the maximum yearly incidence of infections was just below 2,000 (our model predicted just over 3,000 for the real campaign). In 1990, this pre-emptive campaign predicts a total of nearly 800 acute infections, where the real campaign model predicts approximately 2,500. Although the shape is similar for both scenarios, the total numbers are considerable lower in the pre-emptive model. Unfortunately, the vaccines for Hepatitis B have only been available since 1982 (Heymann (2004)), so New Zealand initiating a vaccination campaign in 1985 was the best case scenario for decreasing the impact of this disease.

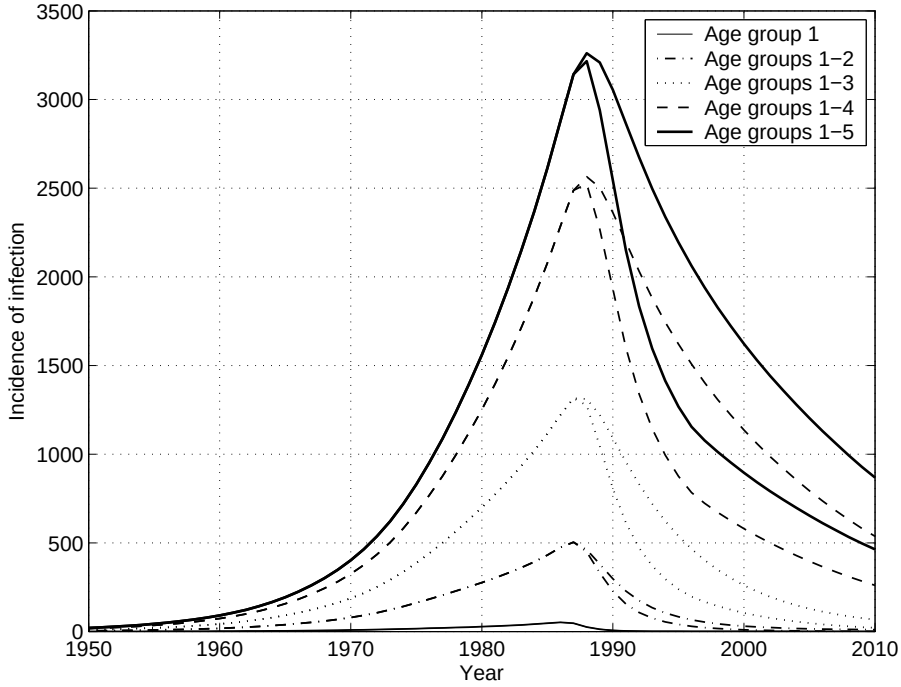


Figure 5.13: The model results for the yearly incidence of infection in cumulative age groups, if only babies were vaccinated (the higher curves after 1985), with the model results for the full vaccination campaign (the lower curves after 1985).

5.4 Parameter Estimation

For all the models we have presented so far, and in our subsequent models, we have not utilised any formal parameter fitting methods. Wherever possible, we have taken our parameters from known data for the infection (for instance the length of time a person remains infectious), but many of the parameters we have estimated. For parameters that relate to the length of time a person is in each compartment, we have used published results to make our estimates. However, for the contact/mixing rates between classes, we have chosen parameters that give us a basic fit to the known data, without using any formal method.

A more formal estimation of the parameters could be carried out using a maximum likelihood method (for example see Powers & Xie (2008) and Johnson & Wichern (2007)) to establish estimates for the mixing/contact parameters, the transmission coefficient (β), and the infectiousness of carriers relative to acutely infected individuals (α). As the data for the incidence of infection are only reliable for the years 1985-2004 (prior to this, both the incidence of infection and any chronic carriers were recorded), we have a small data set to use for our parameter fitting, which could cause a bias in the method. As we have a large number of parameters to estimate, and such a limited data set, we chose not to implement a formal parameter fitting method in all our models.

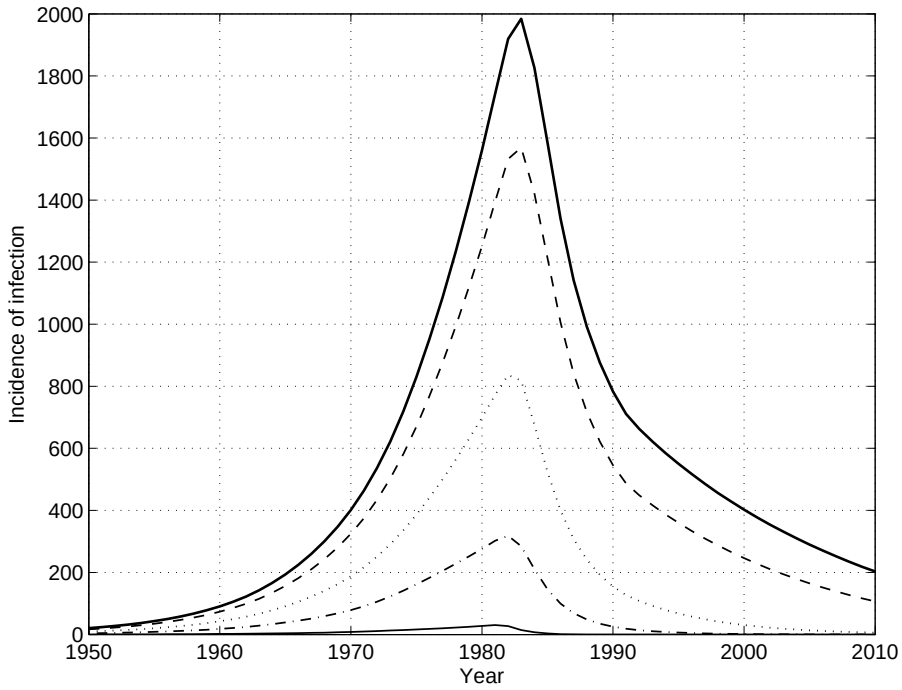


Figure 5.14: The cumulative incidence of infection for the five age classes if the vaccination campaign were started in 1980 (five years before the campaign actually started).

5.5 Conclusions

Data on Hepatitis B infections in New Zealand have only been recorded since 1971 (the virus was only discovered in 1967), giving us a limited amount of data to compare our results to. There is also a limited amount of data available about the length of the carriage state, or the number of carriers in the population. Our five age class model shows a rough fit to the known data, but predicts much higher numbers in cases of infection than were actually seen. However, the number of carriers predicted by the model is low compared to the approximation given in Gane (2005). From our model we can say that the vaccination campaign greatly decreased the number of carriers in our population (by decreasing the number of infections), thus reducing the number of cases of infection to zero by 2100. We were also able to explore the potential effects of a different vaccination scenario, and the effect of the current campaign if it were introduced five years earlier.

New Zealand is classed with a low endemic level of hepatitis B (less than 2 percent level of carriage or endemicity), yet there are areas of medium (2–7 percent) and high (8 percent and over) levels. New Zealand Ministry of Health (2006) states that in 1985 there was evidence of past infection in 15 percent of New Zealand children, but there is also evidence that nearly half of the population in the eastern Bay of Plenty who were infected by age 15. Our models do not differentiate between high and low prevalence areas, but concentrate only on incidence of infection and carriage related to age. Future work to improve our models could be to add a spatial structure to the model with varying rates

of infection, and possibly include the effects of migration from high endemic countries.

We also made the assumption that vaccination did not wane over time, and that immunity through past infection was lifelong. The response to vaccination reduces with the age at which it is administered (New Zealand Ministry of Health, 2006), which could be included in the model. In the literature we reviewed, a number of papers split the population by age groups, male/female, or sexual orientation so that the more "at risk" groups could be targeted separately. For this kind of structure to be included in the New Zealand model, a structure relating to ethnicity would be more appropriate. This structuring of the population would be more comparable to the known data on targeting screening for Hepatitis B (Gane, 2005), and help predict the effect and cost of a more targeting immunisation campaign in the future.

The inclusion of a separate chronic hepatitis disease class would also be a beneficial amendment to our model, as it is this class that requires ongoing care for chronic active hepatitis or cirrhosis. Presently, our model includes these in our carrier compartment, and we have not included any provision for the shortened life expectancy if the chronic condition develops.

The models we have presented can be expanded to be better suited for the New Zealand situation, but already show a good framework on which to construct a fuller model.

Chapter 6

A Mathematical Model of Meningococcal Disease in New Zealand

6.1 Introduction

The first epidemic of meningococcal disease was reported in 1661 by Thomas Willis, yet it was not classified as meningococcal disease then but as an outbreak of "cerebrospinal fever". Vieusseuz is accredited for the first account of a meningococcal epidemic in Geneva and its surroundings in 1805 (Cartwright, 1995; New Zealand Ministry of Health, 2002). It was not until 1887 that the bacterium that causes meningococcal disease, *Neisseria meningitidis*, was identified by Anton Weichselbaum in Vienna (Cartwright, 1995; World Health Organisation, 1998). There have been numerous meningitis epidemics reported during the 20th Century, with major outbreaks during World War I, World War II, and an ongoing epidemic in Africa since 1909 (World Health Organisation, 1998).

Infection with meningococcus can cause a variety of diseases, but the most common are meningitis (the swelling of the membranes and fluid that cover the brain and spinal cord) and/or septicaemia (blood poisoning) (New Zealand Ministry of Health, 2002). Meningococcal disease is caused by a bacterium, *N. meningitidis*, which colonises the upper respiratory tract. There are numerous serogroups of the bacterium, with serogroup B being the causative strain of the New Zealand epidemic. The infection is transmitted by either aerosolised droplets of respiratory secretions, or by contact (e.g. sharing a glass) with these secretions. Once the bacteria have been acquired, they bond to the cells at the back of the throat and nasal passage. The bacteria can then manoeuvre their way into the bloodstream where they may invade and multiply in the cerebrospinal fluid. The colonisation of the nasopharynx can continue for months causing a persistent source of infection to others. In most people, antibodies kill the bacteria before they can cause the disease (Thomas, 2004), however it is possible to carry the meningococci and be infectious

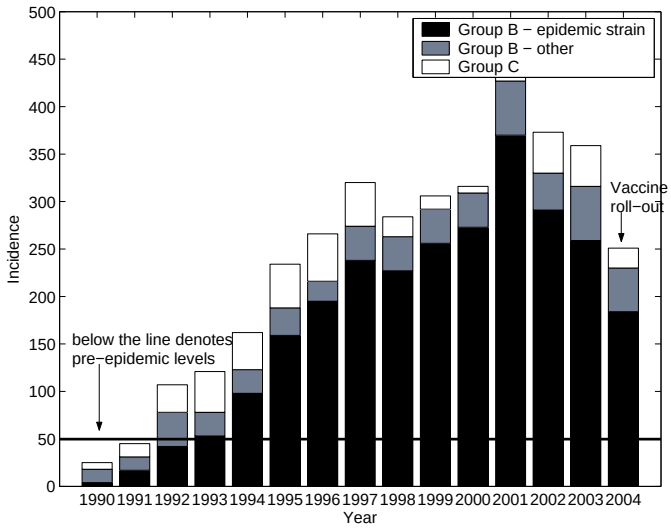


Figure 6.1: The recorded number of meningococcal cases of infection, with data from CBG Health Research Ltd (2006). The group B epidemic strain is responsible for the majority of meningococcal disease cases.

while not showing any symptoms of infection.

Infection with the invasive form of meningococcal disease leads to a quick onset of symptoms including headache, nausea and vomiting, with approximately two-thirds of cases presenting a rash. Acute infection can lead to death within 24 hours. "For every 100 people who get the disease, four will die. Another 20 will be left with some degree of serious disability, such as brain damage, deafness, loss of limbs or damaged skin. A further proportion is left with learning or behavioural difficulties." (New Zealand Ministry of Health, 2004).

New Zealand's epidemic of meningococcal disease began in mid-1991, and in 2004 an immunisation program was introduced in the hope of ending the epidemic. The annual number of meningococcal cases can be seen in Figure 6.1, noting that the epidemic strain is responsible for the majority of cases in New Zealand. On average, 80% of cases of meningococcal disease occur in people aged 0-19 years, and within this age group the majority of these cases are seen in under five year olds (New Zealand Ministry of Health, 2004), shown in Figure 6.2. We can use a mathematical model to investigate the impact of the vaccination scheme on the epidemic patterns, and investigate the potential outcomes of alternate vaccination strategies. To do so, we first need to develop a mathematical model of the number of acute infections and carriers of the infection, then compare this to the known history of the epidemic in New Zealand. We present a brief overview of models that have already been completed, and then formulate a model that is most appropriate for the New Zealand epidemic.

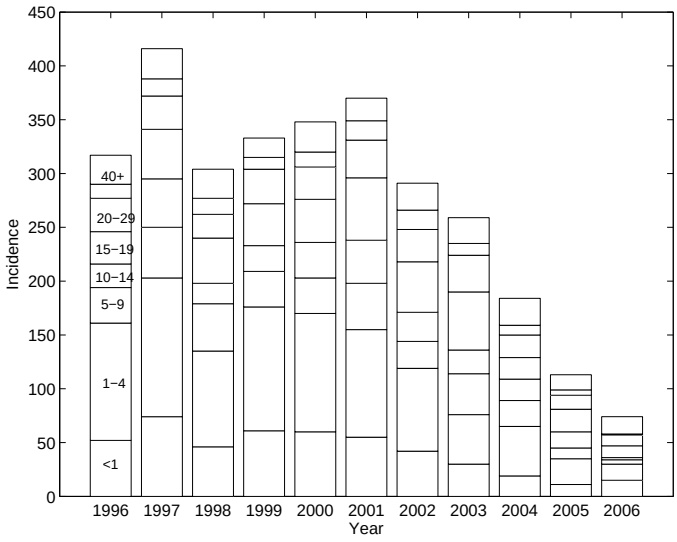


Figure 6.2: The recorded number of meningococcal epidemic strain cases of infection, with data from Kieft *et al.* (2001) and Martin *et al.* (2007). The lowest bar represents cases in infants less than one year old, the second bar 1–4 year olds, then 5–9 year olds, 10–14, 15–19, 20–29, 30–39, then over 40 year olds. The largest number of cases are seen in the 1–4 year old age group.

6.2 Literature Review

There are a number of mathematical models of meningococcal disease, with many of them looking at the bacterial level of the infection process and then a smaller portion modelling the spread and control of the disease. To date, we are unaware of any mathematical modelling papers published specifically looking at the New Zealand meningitis epidemic, as the majority of published models take their data from epidemics and vaccination campaigns in Europe and the United States.

One of the interesting features of meningococcal disease is that there is a carriage state, where a person is infected and infectious, but shows no signs of illness, which is something that we feel should be allowed for in a model, making it somewhat similar to infections such as Hepatitis B. Tuckwell *et al.* (2003) have not included a carriage state in their model and assumed that the infection was at steady state with carriers and non-carriers in equilibrium. Meyers *et al.* (2001) do not explicitly include a carrying population, but they have two strains of infection - one that is more likely to cause the invasive form of the infection and one that is likely to stay benign. Trotter & Gay (2003) only considered the population to be in two states: those carrying the infection and those not. However, their paper is mainly concerned with the sensitivity of techniques used to identify whether the infection is present in carriers and the infection and recovery rate, rather than with the actual spread of the infection in the population.

As a large number of cases are seen in the under twenty year old age bracket, sectioning the population into age classes would be beneficial when creating a model. Tuckwell *et al.*

(2003); Coen *et al.* (2000); Guinea *et al.* (2005); Martcheva & Crispino-O'Connell (2003); Trotter & Gay (2003) and Trotter *et al.* (2006) all included age structure in their models. Tuckwell *et al.* (2003) state that the most effective vaccination campaign over a 10 year period is to immunise all of the population aged between 2 and 20 years. Trotter *et al.* (2005, 2006) showed that the most effective campaign targeted teenagers thus maximising the herd immunity, and therefore reducing the prevalence of carriage to an extent that it took years to recover.

Stollenwerk and co-workers have published a number of papers on the modelling of invasive meningococcal disease, see: Stollenwerk *et al.* (2004); Stollenwerk & Jansen (2003a,b) and Guinea *et al.* (2005). They implemented an SIRYX model, in which the I class are those infected with a benign strain of meningococcal disease (which can be seen as carriers), the Y class are those infected with a mutant strain of the infection that can cause acute infection, and class X are the severely affected hosts. Those in the acutely infected class cannot infect others, but can return to the susceptible class. Carriers, I class, can develop the mutant strain of infection and become Y class, but the chance of this is extremely small. From the I and Y classes, individuals become removed, but the removed class then feeds back into the susceptible class. There is no age structure included in their models, and all the models are implemented stochastically using a Markov process. A constant population size is imposed, with 25% of the population being in the benign carriage class, I, at any time. The average duration of both carriage and immunity is ten months. By letting there be seasonal changes in transmission, the model produces seasonal changes in the carriage rates which lead to variations in the incidence of disease. Yet, the seasonality in transmission did not yield any variation in the yearly incidence rate unless both the benign and the mutant strain were present. It is this diversity in the strains of disease that the authors conclude are crucial for epidemics of meningococcal disease to occur.

Trotter and co-workers also published a number of papers on modelling meningococcal disease in England and Wales, and looked at the impact of the vaccine against the epidemic strain (Trotter *et al.* (2006); Trotter & Gay (2003) and Trotter *et al.* (2005)). They split the population into nine compartments: susceptible and un-vaccinated; susceptible and routinely vaccinated; susceptibles vaccinated during a catch-up campaign; un-vaccinated carriers; carriers who were vaccinated during one of the catch-up campaigns; un-vaccinated carriers of other strains of meningococcal; routinely vaccinated carriers of other strains of meningococcal and carriers of other meningococcal who were vaccinated during a catch-up campaign. The effects of vaccination wane over time, and the model allows an individual to be a carrier a multiple number of times for any strain of meningococcal. They split the population into 75 one year age cohorts, and let the prevalence of carriage be dependent on age with low prevalence in young children and peaking in teenagers, and implement their model using differential equations. They do not explicitly model the invasive meningococcal disease, but calculate the incidence based on carriers. They

assume that co-infection with more than one strain of meningococcal is not possible, and that the duration of carriage is only 3 months (this is decreased to better fit the model to the known data). Their model produces a good fit to the England and Wales epidemic data, with an estimated basic reproduction ratio of 1.36. Trotter *et al.* (2005) look at various vaccination campaigns, and conclude that the most effective use of vaccination is to target teenagers to generate herd immunity in the population.

Tuckwell *et al.* (2003) give a difference equation model with discrete time and monthly age groups for the effects of vaccination on a non-specific disease, which they then apply to meningococcal disease. The population is compartmentalised according to their immune status: never vaccinated; non–susceptible; unsuccessful vaccination; non-fatal case; death from disease and death from other causes. All births go into the susceptible compartment, and immunity results from non-fatal infection or from successful vaccination. Carriers of the infection are not specifically included in the model, they assume a steady state where the carriers and non-carriers are in equilibrium, and the per capita rates of fatal and non-fatal cases are fixed – which implies that these rates are small relative to the overall birth and death rates, so the carriage rates do not change significantly. This lack of change in carriage rates has been noted in most of the models, with the assumption that a certain percentage of the population is always in a carrier state. They apply various vaccination schedules and use parameter estimates from an epidemic of meningococcal C disease in France. The best vaccination schedule, in regard to number of deaths and cases of infection avoided, is by vaccinating everyone in the population between 2 and 20 years old – which is the best scheme other than to vaccinate the entire population. However, the scheme in which only one year olds are vaccinated also performs as well in terms of cases avoided, but not deaths avoided per dose of vaccine.

Meyers *et al.* (2003) and Coen *et al.* (2000) both look at modelling with two strains of infection. Meyers *et al.* (2003) use two different strains of meningococcal, a fast phase-shifting strain and a wild strain with limited or no phase shifting. The fast phase shifting strain is the one that causes the invasive disease, where the wild strain is the carrier strain. They present two models, first where the population is split into two groups with respect to the strains and a second model where secondary infection is allowed with a different strain. The paper is mostly concerned with the with-in host infection dynamics, and the need of the two strains to cause an epidemic, and does not compare their findings to known data. Coen *et al.* (2000) look at meningococcal disease and carriage, as well as carriage of *Neisseria lactamica* which is a related organism to *N. meningitidis*. They present three models for the incidence of carriage and of disease, and use an estimated duration of carriage of 13.3 months, based on data from Belgian school children. The model that best fits their known data, was one that has acquisition of meningococcal carriage inhibited by carriage of *N. lactamica*, and carriage rates dependant on age, with infants having the greatest pre-carriage rates of illness.

An age structured partial differential equation model is presented by Martcheva &

Crispino-O'Connell (2003), with the population split into four compartments in relation to the infection: susceptible, infected, carrier and temporarily immune. Everyone is born immune to infection, and then lose that immunity to become susceptible at an average age of three months. Martcheva & Crispino-O'Connell assume an age distribute rate of carriage, which peaks at 45% in teenagers and young adults. There is no immunity in the model (apart from at birth), either from infection or from carriage, and there is no mortality rate due to infection. The paper looks at the stability of the disease free state, the existence and stability of the endemic equilibrium, and the persistence of the disease, but not at the solutions of the model and does not make any comparison to known data.

All of the papers mentioned here are based on epidemic data from outside New Zealand, and not for the B strain of the disease. To create a model specifically for New Zealand, we can utilise some of the ideas and assumptions made in other papers, then include the vaccination campaign that has been initiated and the long-time span of the epidemic.

6.3 SCIR Model

We can think of the population as being split into four distinct compartments: the proportion of the population who are susceptible to infection (s); those who are carrying the infection and are infectious, but show no signs of the invasive disease (c); those who have the invasive disease and are still infectious (i); and those who are "removed" - no longer take part in the infection cycle due to immunity (r). We assume that you cannot die directly from the disease.

From being susceptible you may become either a carrier or invasively infected after contact with someone in either of these compartments. Once in the carriage compartment, you may move to the invasively infected or removed compartment, and once invasively infected there is only movement to the removed compartment. From each compartment there is a natural death rate from causes other than the infection and we have assumed a constant population with the birth and death rates being equal (as death from the infection is not taken into consideration). This is shown in Figure 6.3 and the system of Equations (6.1) below:

$$\begin{aligned}
\frac{ds}{dt} &= -\beta s(i+\alpha c) - \mu s + \mu \\
\frac{dc}{dt} &= \beta sp(i+\alpha c) - c(\gamma_1 + \sigma + \mu) \\
\frac{di}{dt} &= (1-p)\beta(i+\alpha c)s + \sigma c - i(\gamma_2 + \mu) \\
\frac{dr}{dt} &= \gamma_1 c + \gamma_2 i - \mu r
\end{aligned} \tag{6.1}$$

We call $\lambda = \beta(i+\alpha c)$ the force of infection, where β is the transmission coefficient, and α is the infectiousness of carriers relative to invasively infected individuals. Respectively,

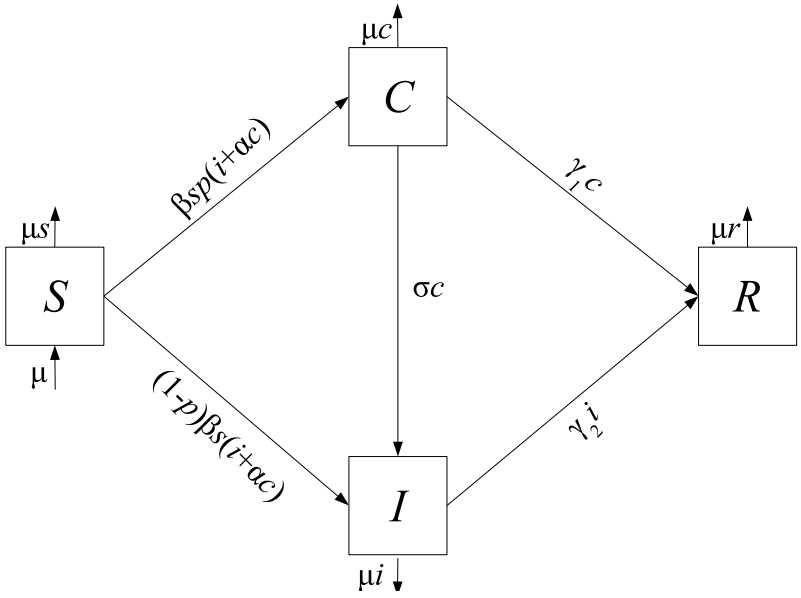


Figure 6.3: Flow diagram for susceptible, carriage, infection and recovery process. The rates of change between each compartment are given.

γ_1 and γ_2 are the rates (per year) at which carriers and invasively infected people recover. p is the proportion of those infected that become carriers; and σ is the rate (per year) at which carriers become invasively infected. μ is the birth/death rate. Table 6.1 shows the values of the model parameters.

We assume that people cannot recover from the carriage state or infected state and return to the susceptible population - i.e. once infected you can not be re-infected. We also have one redundant equation, as the population size remains constant.

We can solve the system of equations numerically using MATLAB, using the parameter values given in Table 6.1. Initially we let 10% of the population be in the carriage state and the rest of the population be in the susceptible state, as shown in Figure 6.4. This model demonstrates that when meningococcal disease is introduced into the population we initially have a large spike in the number of invasive infections and carriers. This then settles down to a steady state, where the infection is still present, but there is a higher proportion of the population in the carriage state, as opposed to the invasive infection state. However, changing some of the parameter values, we can introduce more complex behaviour into our model as shown in Figure 6.5: we see fluctuations in the proportion of susceptibles and carriers; and minor fluctuations in the proportion of infectious people before settling down to an endemic steady state.

Analysis of the simple SCIR model

To analyse this model, we calculate the basic reproduction ratio, then check the consistency of the next generation matrix by calculating the Jacobian at the trivial steady state. The

Parameter	Description	Units	Value
α	infectiousness of carriers relative to invasively infected.	proportion	0.8
μ	birth/death rate.	per year	0.0125
p	proportion of the people infected who become carriers.	proportion	0.9
γ_1	rate at which carriers recover.	per year	0.3
σ	rate at which carriers become invasively infected.	per year	0.001
γ_2	rate at which invasively infected people recover.	per year	0.1

Table 6.1: Description of parameters used in the model, with values used in the examples.

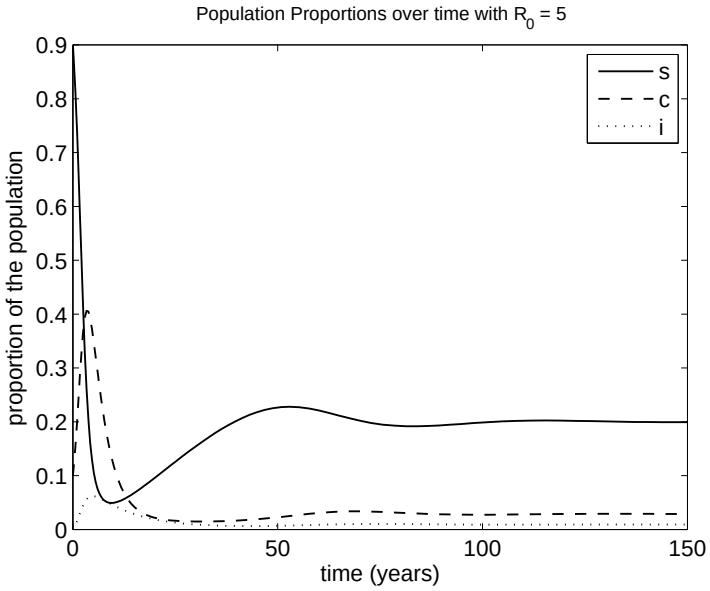


Figure 6.4: The proportion of the population in each compartment over time. Initially $s = 0.9$, $c = 0.1$ and $i = 0$. Parameter values listed in Table 6.1.

stability of the steady state should change as R_0 passes through one, therefore the Jacobian matrix should have a zero eigenvalue when $R_0 = 1$. We will use this method to check the consistency of our next generation matrix in all our following models.

The measure of spread of an infection is the basic reproduction ratio, R_0 - that is: the expected number of secondary cases that would occur from a primary case in a fully susceptible population (Anderson & May, 1992; Diekmann & Heesterbeek, 2000). To calculate R_0 we first need the next generation matrix which describes the expected number of secondary cases that would occur from a primary case in a fully susceptible population in each category. For our model we require a 2×2 next generation matrix, the first column representing the number of secondary cases that would occur due to a primary infectious

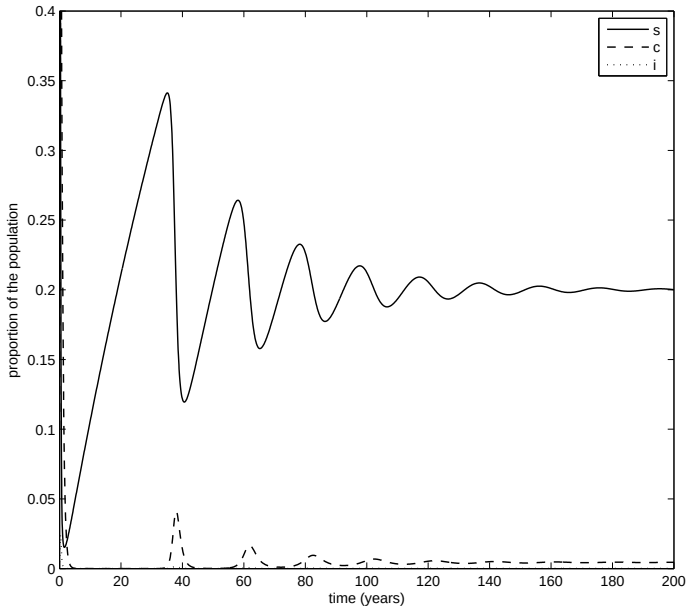


Figure 6.5: The proportion of the population in each compartment over time. Initially $s = 0.9$, $c = 0.1$ and $i = 0$. Parameter values: $\gamma_1 = 2$, $\sigma = 0.01$, $\gamma_2 = 7$ and all other values as in Table 6.1.

carrier, and the second column representing the number of secondary cases that would occur due to a primary invasive infectious person. Then

$K_{1,1}$: Carrier hosts infect others at rate $\beta\alpha$ and remain infectious for $\frac{1}{\gamma_1+\sigma+\mu}$ years. A proportion $\frac{\sigma}{\gamma_1+\sigma+\mu}$ of carriers go on to become infected hosts, who in turn infect people at rate β and remain infectious for $\frac{1}{\gamma_2+\mu}$ years. A proportion p of those infected go on to become carriers.

$K_{1,2}$: Invasively infected hosts infect others at rate β and remain infectious for $\frac{1}{\gamma_2+\mu}$ years. A proportion, p of those infected then become carrier hosts.

$K_{2,1}$: Carrier hosts infect others at rate $\beta\alpha$ and remain infectious for $\frac{1}{\gamma_1+\sigma+\mu}$ years, then a proportion $1-p$ of those infected go on to become invasively infected hosts. A proportion σ of carriers go on to become invasively infected hosts, who in turn infect people at rate β and remain infectious for $\frac{1}{\gamma_2+\mu}$ years.

$K_{2,2}$: Invasively infected hosts infect others at rate β and remain infectious for $\frac{1}{\gamma_2+\mu}$ years. A proportion, $1-p$ of those infected then go on to be invasively infected.

Hence, the next generation matrix is:

$$K = \begin{pmatrix} \frac{\beta p}{\gamma_1+\sigma+\mu}\left(\alpha + \frac{\sigma}{\gamma_2+\mu}\right) & \frac{\beta p}{\gamma_2+\mu} \\ \frac{\beta(1-p)}{\gamma_1+\sigma+\mu}\left(\alpha + \frac{\sigma}{\gamma_2+\mu}\right) & \frac{(1-p)\beta}{\gamma_2+\mu} \end{pmatrix} \tag{6.2}$$

The basic reproduction ratio is the largest eigenvalue of the next generation matrix (as this matrix has linearly dependent rows, we see that this is just the trace):

$$R_0 = \frac{\beta((\mu+\gamma_1)(1-p)+p\alpha(\mu+\gamma_2)+\sigma)}{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)} \tag{6.3}$$

To find the steady states, we first note that as the population is of constant size we have one redundant equation in the system given in Equation (6.1). We work with the first three equations only. Setting the derivatives to zero, we can re-write the steady state equations as a linear matrix equation:

$$\beta s^* \begin{pmatrix} p & \alpha p \\ 1-p & (1-p)\alpha \end{pmatrix} \begin{pmatrix} i^* \\ c^* \end{pmatrix} = \begin{pmatrix} 0 & \gamma_1+\sigma+\mu \\ \gamma_2+\mu & -\sigma \end{pmatrix} \begin{pmatrix} i^* \\ c^* \end{pmatrix}$$

By taking the inverse of the matrix on the right hand side and rearranging, we gain the following:

$$\beta \begin{pmatrix} \frac{\sigma p}{(\sigma+\gamma_1+\mu)(\gamma_2+\mu)} + \frac{1-p}{\gamma 2+\mu} & \frac{\sigma\alpha p}{(\sigma+\gamma_1+\mu)(\gamma 2+\mu)} + \frac{\alpha(1-p)}{\gamma 2+\mu} \\ \frac{p}{\sigma+\gamma_1+\mu} & \frac{\alpha p}{\sigma+\gamma_1+\mu} \end{pmatrix} \begin{pmatrix} i^* \\ c^* \end{pmatrix} = \frac{1}{s^*} \begin{pmatrix} i^* \\ c^* \end{pmatrix}$$

We see that s^* is the inverse of the non-zero eigenvalue of the previous matrix, and we know that there is also the trivial solution, so:

$$\begin{aligned} s^* &= 1 \\ s^* &= \frac{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)}{\beta((\mu+\gamma_1)(1-p)+p\alpha(\mu+\gamma_2)+\sigma)} = \frac{1}{R_0} \end{aligned} \tag{6.4}$$

Thus there are only two steady states for this system of equations, one where there is no infection present in the population $(s,i,c) = (1,0,0)$, and an endemic steady state, (s^*,i^*,c^*). We find the endemic steady state values for the carrier and invasively infected populations by substituting $s^* = \frac{1}{R_0}$ in Equations (6.1) and setting the derivatives to zero. From $\frac{ds}{dt} = 0$, with $\lambda = \beta(c^* + \alpha^*)$ we gain:

$$i^* = \frac{\mu(1-s^*)}{\beta s^*} - \alpha c^* \tag{6.5}$$

Then using this in Equation (6.1) for the carriers, we get a solution for c^*:

$$c^* = \frac{p\mu(1-s^*)}{\sigma+\gamma_1+\mu} \tag{6.6}$$

Thus, the non-trivial steady state is given by:

$$(s^*,c^*,i^*) = \left(\frac{1}{R_0}, \frac{p\mu\left(1-\frac{1}{R_0}\right)}{\sigma+\gamma_1+\mu}, \mu\left(1-\frac{1}{R_0}\right)\left(\frac{R_0}{\beta} - \frac{\alpha}{\sigma+\gamma_1+\mu}\right)\right) \tag{6.7}$$

To determine the stability of the steady states we construct the Jacobian matrix. To see if our system changes stability at the trivial steady state, we calculate the eigenvalues

of the Jacobian at the trivial steady state, and compare these to R_0 at the trivial steady state. The Jacobian for the system of Equations (6.1) is given by:

$$J = \begin{pmatrix} -\beta(i+\alpha c) - \mu & -\beta s\alpha & -\beta s \\ \beta p(i+\alpha c) & \beta sp\alpha - \gamma_1 - \sigma - \mu & \beta sp \\ (1-p)\beta(i+\alpha c) & (1-p)\beta s\alpha + \sigma & (1-p)\beta s - \gamma_2 - \mu \end{pmatrix}$$

At the trivial steady state ($s = 1$, $c = i = 0$) the Jacobian becomes:

$$J_1 = \begin{pmatrix} -\mu & -\beta\alpha & -\beta \\ 0 & \beta p\alpha - \gamma_1 - \sigma - \mu & \beta p \\ 0 & (1-p)\beta\alpha + \sigma & (1-p)\beta - \gamma_2 - \mu \end{pmatrix}$$

We can re-write this as:

$$\begin{aligned} J_1 &= \begin{pmatrix} 0 & -\beta\alpha & -\beta \\ 0 & \beta p\alpha & \beta p \\ 0 & (1-p)\beta\alpha + \sigma & (1-p)\beta \end{pmatrix} - \begin{pmatrix} \mu & 0 & 0 \\ 0 & \gamma_1 + \sigma + \mu & 0 \\ 0 & 0 & \gamma_2 + \mu \end{pmatrix} \\ &= \tilde{J}_1 - D \end{aligned} \tag{6.8}$$

Suppose that J_1 has an eigenvalue ω with corresponding eigenvector x, then:

$$\begin{aligned} J_1 x &= \omega x \\ (\tilde{J}_1 - D)x &= \omega x \\ (D + I\omega)^{-1}\tilde{J}_1 x &= x \end{aligned} \tag{6.9}$$

We see that $(D + I\omega)^{-1}\tilde{J}_1$ has an eigenvalue of 1. Letting $\omega = 0$ the characteristic polynomial of $D^{-1}\tilde{J}_1$ is:

$$\begin{aligned} u^2 - u\beta\left(\frac{\alpha p(\gamma_2+\mu) + (1-p)(\gamma_1+\sigma+\mu)}{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)}\right) - \frac{\beta p\sigma}{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)} &= 0 \\ u^2 - u(f+g) - h &= 0 \end{aligned} \tag{6.10}$$

where $f = \frac{\beta\alpha p(\gamma_2+\mu)}{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)}$, $g = \frac{\beta(1-p)(\gamma_2+\sigma+\mu)}{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)}$ and $h = \frac{\beta p\sigma}{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)}$.

The characteristic polynomial for the next generation matrix, K, is:

$$\begin{aligned} v\left(v - \beta\frac{(\mu+\gamma_1)(1-p) + p\alpha(\mu+\gamma_2) + \sigma}{(\gamma_1+\sigma+\mu)(\gamma_2+\mu)}\right) &= 0 \\ v(v - (f+g+h)) &= 0 \end{aligned} \tag{6.11}$$

From the previous two Equations (6.10) and (6.11) we see $u = 1 \Leftrightarrow v = 1$, thus if the Jacobian at the trivial steady state has an eigenvalue of zero, then the next generation matrix has an eigenvalue of one.

We can show numerically that when the next generation matrix has eigenvalues less than one (meaning that $R_0 < 1$ and the infection cannot persist in the population) then the Jacobian at the trivial steady state has negative eigenvalues - so the trivial steady state

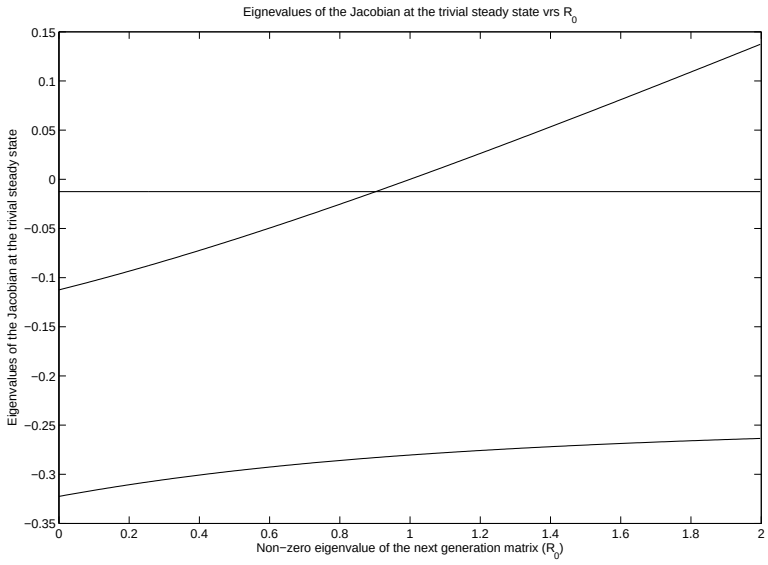


Figure 6.6: The eigenvalues of the Jacobian matrix for the simple SCIR model plotted against the non-zero eigenvalue of the next generation matrix (R_0). We can see that when $R_0 < 1$ the eigenvalues of J_1 are all negative, indicating that the trivial steady state ($s = 1$, $c = i = 0$) is stable.

is stable (shown in Figure 6.6). We have a transcritical bifurcation when $R_0 = 1$ (as can be seen in Figure 6.7): the steady state relating to no infection in the population changes from stable to unstable and the endemic steady state appears and is stable. We see that as the basic reproduction ratio increases the proportion of susceptibles in our population at the steady state decreases towards, but never actually reaches zero. The unstable steady state when $R_0 < 1$ shown in Figure 6.7, does not make sense biologically as the proportion of the population susceptible is greater than one, but it is mathematically present and we can prove it is unstable.

This model captures the main characteristics of an epidemic of meningococcal disease, however it does not include the fact that a large proportion of the cases that are seen in New Zealand occur in the under 5 years old age group. With this is mind, we now expand our model to have a population split into five age groups, so that we can look more closely at what is happening at the age group level, and tailor our model to reflect any differences that occur in disease transmission in each of the age groups. This will also allow us to include the affect of vaccination more easily, and compare our model results to known data. Also, as we have calculated this in terms of proportion of the population infected, it is hard to compare this to the known number of cases recorded, so we now change to deal in number of people infected.

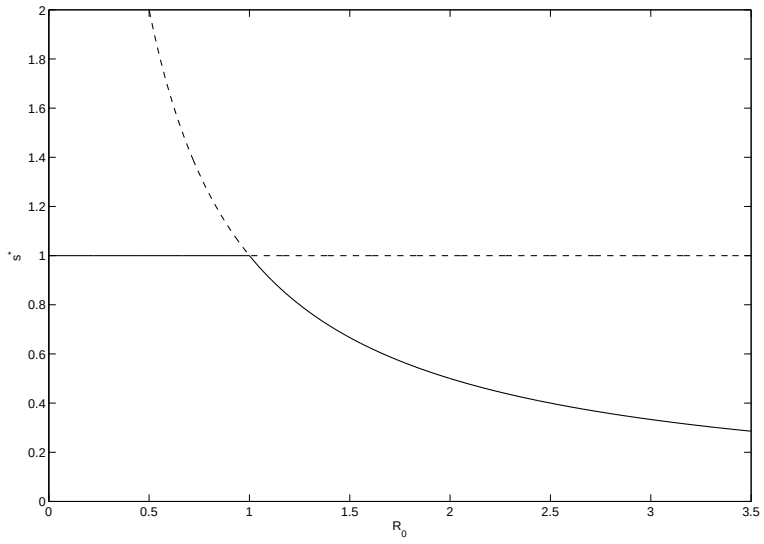


Figure 6.7: Bifurcation diagram for the simple SCIR proportion model, with the bifurcation when $R_0 = 1$ - the solid lines represent the stable steady state, and the dashed lines the unstable steady state. When $R_0 < 1$ the trivial steady state is stable, meaning that an infection will not persist in the population. For $R_0 > 1$, the non-trivial steady state becomes stable, so an infection will persist in the population. As R_0 increases, we see that the number of people that remain susceptible at the steady state decreases.

6.4 Structured SCIR Model

We now split our population into 5 age classes: class 1: new born – 1 year old; class 2: 1–10 years old; class 3: 10–20 years old; class 4: 20–40 years old and class 5: 40–70 year old. We have chosen these age classes to align with the recorded data for the number of infections each year. We have again split our population into four distinct compartments for each age class, but this time looking at the number of people in each compartment, rather than proportion: S_i is the number of susceptibles in age class i; C_i is the number of carriers in age class i; I_i is the number of infected people in age class i and R_i is the number of recovered or immune people in age class i. This is an extension of our previous model, but we have allowed for non-homogeneous mixing between the age classes: m_{jk}, is the mixing rate between age classes j and k, shown in Equation (6.15). A schematic of the infection process can be seen in Figure 6.8.

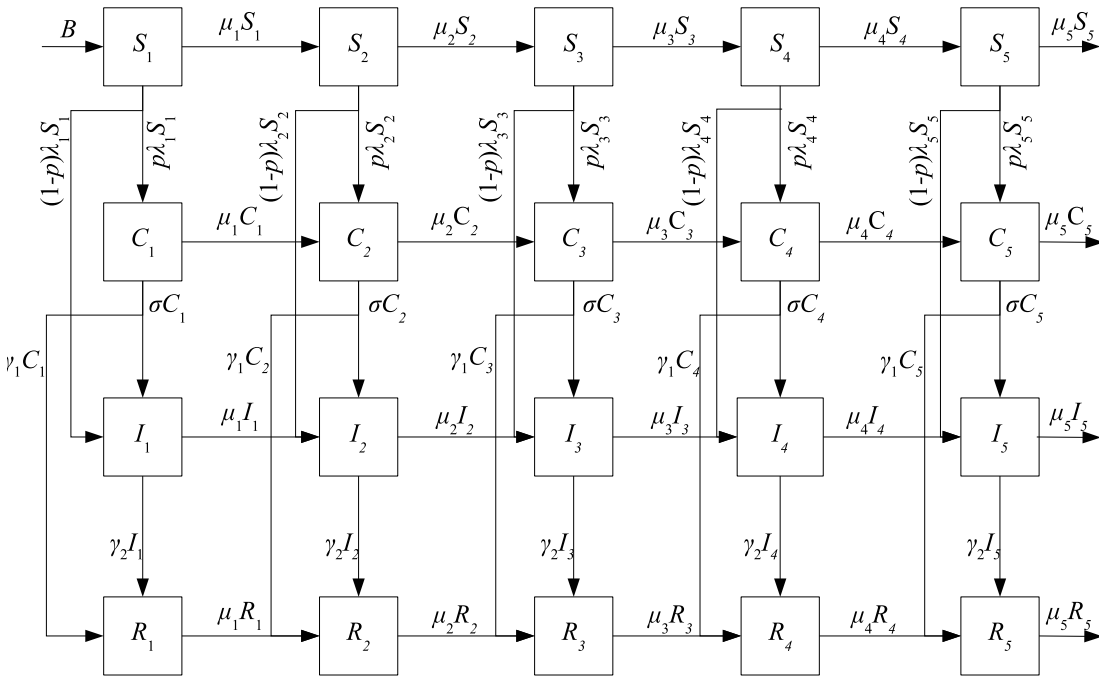


Figure 6.8: Flow diagram for the meningococcal disease infection process, when the population is split into five age classes.

$$\text{group 1 (0–1 year)} \begin{cases} \frac{dS_1}{dt} = B - (\lambda_1 + \mu_1)S_1 \\ \frac{dC_1}{dt} = p\lambda_1 S_1 - (\sigma + \gamma_1 + \mu_1)C_1 \\ \frac{dI_1}{dt} = (1-p)\lambda_1 S_1 + \sigma C_1 - (\gamma_2 + \mu_1)I_1 \\ \frac{dR_1}{dt} = \gamma_1 C_1 + \gamma_2 I_1 - \mu_1 R_1 \end{cases} \tag{6.12}$$

$$\text{groups 2–5} \begin{cases} \frac{dS_j}{dt} = \mu_{j-1}S_{j-1} - (\lambda_j + \mu_j)S_j \\ \frac{dC_j}{dt} = \mu_{j-1}C_{j-1} + p\lambda_j S_j - (\sigma + \gamma_1 + \mu_j)C_j \\ \frac{dI_j}{dt} = \mu_{j-1}I_{j-1} + (1-p)\lambda_j S_j + \sigma C_j - (\gamma_2 + \mu_j)I_j \\ \frac{dR_j}{dt} = \mu_{j-1}R_{j-1} + \gamma_1 C_j + \gamma_2 I_j - \mu_j R_j \end{cases} \tag{6.13}$$

where

$$\lambda_j = \frac{\beta}{N}\sum_{k=1}^{5} m_{jk}(I_k + \alpha C_k) \tag{6.14}$$

The parameter values and their descriptions for this model are shown in Table 6.2.

Parameter	Description	Value
B	birth rate	64460 people per year
α	infectiousness of carriers relative to invasively infected.	1
μ_1	rate at which age class 1 moved to age class 2	1 year^{-1}
μ_2	rate at which age class 2 moved to age class 3	$\frac{1}{10-1}$ year^{-1}
μ_3	rate at which age class 3 moved to age class 4	$\frac{1}{20-10}$ year^{-1}
μ_4	rate at which age class 4 moved to age class 5	$\frac{1}{40-20}$ year^{-1}
μ_5	death rate of age class 5	$\frac{1}{70-40}$ year^{-1}
p	proportion of the people infected who become carriers.	0.99
γ_1	rate at which carriers recover.	2 year^{-1}
σ	rate at which carriers become invasively infected.	0.0001 year^{-1}
γ_2	rate at which invasively infected people recover.	10 year^{-1}
β	transmission coefficient	refer to text

Table 6.2: Description of parameters used in the model, with values used in the examples.

We use similar mixing rates to Roberts & Tobias (2000) as meningococcal is spread in a similar manner to measles ($a_1 = 1$, $a_2 = 5$, $a_3 = 5$, $a_4 = 2$, $a_5 = 1$ and $\epsilon = 0.4$). This is a mixture of preferential mixing (where the off diagonal entries would be zero), and proportionate mixing (the mixing between groups is proportionate the the activity levels of these groups). The parameter ϵ adds a weighting to the proportionate mixing, letting

the mixing between two age classes be damped down slightly.

$$m = \begin{bmatrix} a_1 & \epsilon\sqrt{a_1a_2} & \epsilon\sqrt{a_1a_3} & \epsilon\sqrt{a_1a_4} & \epsilon\sqrt{a_1a_5} \\ \epsilon\sqrt{a_2a_1} & a_2 & \epsilon\sqrt{a_2a_3} & \epsilon\sqrt{a_2a_4} & \epsilon\sqrt{a_2a_5} \\ \epsilon\sqrt{a_3a_1} & \epsilon\sqrt{a_3a_2} & a_3 & \epsilon\sqrt{a_3a_4} & \epsilon\sqrt{a_3a_5} \\ \epsilon\sqrt{a_4a_1} & \epsilon\sqrt{a_4a_2} & \epsilon\sqrt{a_4a_3} & a_4 & \epsilon\sqrt{a_4a_5} \\ \epsilon\sqrt{a_5a_1} & \epsilon\sqrt{a_5a_2} & \epsilon\sqrt{a_5a_3} & \epsilon\sqrt{a_4a_5} & a_5 \end{bmatrix} \tag{6.15}$$

We calculate the next generation matrix for this model by considering it as a sum of matrices - the first matrix is a next generation matrix that does not include the demographics of our population (so we will leave out the inter-age compartment changes), and then subsequent matrices include the demographic changes. Each matrix is a 10×10 matrix, as there are ten types of infection: either carrier or infectious in each of our five age classes. Each column of the matrix represents who caused the infection, and each row of the matrix represents what type of infection was caused. Columns/rows $1 \ldots 5$ are from/to C_i and columns/rows 6..10 are from/to I_i. We let K^0 be the matrix that does not take into account any demographics, K^1 will be the demographic adjustment for one change in age class, K^2 will the be the demographic adjustment for a change over two age classes and K^j will be the matrix with demographic adjustment for change over j age classes.

Considering K^0, we can easily split this into four parts, each being a 5×5 sub-matrix:

$$K^0 = \begin{pmatrix} A & B \\ C & D \end{pmatrix} \tag{6.16}$$

The upper left sub-matrix of K^0, A, will be expected number of carriers caused by carriers for all the age class combinations. Carriers infect others at rate $\frac{\alpha\beta}{N}$ and remain carriers (of age class i) for an average of $\frac{1}{\sigma+\gamma_1+\mu_i}$ years. They mix with age class j at rate m_{ij} and pS_j^* of those infected go on to become carriers. A proportion, $\frac{\sigma}{\sigma+\gamma_1+\mu_i}$, of carriers can also go on to become acutely infected individuals who will infect others at rate $\frac{\beta}{N}$ and remain infectious for $\frac{1}{\gamma_2+\mu_i}$ years. They mix with age class j at rate m_{ij} and a proportion p of those they have infected will go on to be carriers. Thus, the upper left 5×5 sub-matrix will have entries of the form $\frac{\beta S_j^*}{N} \frac{m_{ij}p}{\sigma+\gamma_1+\mu_i} \left(\alpha + \frac{\sigma}{\gamma_2+\mu_i}\right)$.

$$A = \frac{\beta p}{N} \begin{pmatrix} \frac{S_1^* m_{11}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_1^* m_{12}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_1^* m_{13}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_2^* m_{21}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_2^* m_{22}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_2^* m_{23}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_3^* m_{31}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_3^* m_{32}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_3^* m_{33}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_4^* m_{41}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_4^* m_{42}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_4^* m_{43}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_5^* m_{51}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_5^* m_{52}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_5^* m_{53}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \end{pmatrix}$$
$$\begin{pmatrix} \frac{S_1^* m_{14}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_1^* m_{15}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_2^* m_{24}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_2^* m_{25}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_3^* m_{34}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_3^* m_{35}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_4^* m_{44}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_4^* m_{45}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_5^* m_{54}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_5^* m_{55}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \end{pmatrix} \tag{6.17}$$

The lower left 5×5 sub-matrix of K^0 represents infectious individuals caused by carrier individuals for all the age class combinations. This is similar to the upper left 5×5, but a proportion $(1-p)S_j^*$ go on to become infectious, so the entries look like $\frac{\beta S_j^*}{N}\frac{m_{ij}(1-p)}{\sigma+\gamma_1+\mu_i}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_i}\right)$.

$$C = \frac{\beta(1-p)}{N} \begin{pmatrix} \frac{S_1^* m_{11}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_1^* m_{12}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_1^* m_{13}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_2^* m_{21}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_2^* m_{22}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_2^* m_{23}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_3^* m_{31}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_3^* m_{32}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_3^* m_{33}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_4^* m_{41}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_4^* m_{42}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_4^* m_{43}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \\ \frac{S_5^* m_{51}}{\sigma+\gamma_1+\mu_1}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_1}\right) & \frac{S_5^* m_{52}}{\sigma+\gamma_1+\mu_2}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_2}\right) & \frac{S_5^* m_{53}}{\sigma+\gamma_1+\mu_3}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_3}\right) \end{pmatrix}$$
$$\begin{pmatrix} \frac{S_1^* m_{14}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_1^* m_{15}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_2^* m_{24}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_2^* m_{25}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_3^* m_{34}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_3^* m_{35}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_4^* m_{44}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_4^* m_{45}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \\ \frac{S_5^* m_{54}}{\sigma+\gamma_1+\mu_4}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_4}\right) & \frac{S_5^* m_{55}}{\sigma+\gamma_1+\mu_5}\left(\alpha+\frac{\sigma}{\gamma_2+\mu_5}\right) \end{pmatrix} \tag{6.18}$$

The upper right 5×5 sub-matrix of K^0 represents carrier infections caused by infectious individuals. Infectious individuals infect susceptibles at rate β and remain infectious (in age class i) for an average of $\frac{1}{\gamma_2+\mu_i}$ years. They mix with age class j at rate m_{ij} and a proportion p of those infected go on to become carriers. So the entries will be of the form $\frac{\beta S_j^* p}{N(\gamma_2+\mu_i)} m_{ij}$.

$$B = \frac{\beta p}{N} \begin{pmatrix} \frac{S_1^* m_{11}}{\gamma_2+\mu_1} & \frac{S_1^* m_{21}}{\gamma_2+\mu_2} & \frac{S_1^* m_{31}}{\gamma_2+\mu_3} & \frac{S_1^* m_{41}}{\gamma_2+\mu_4} & \frac{S_1^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_2^* m_{11}}{\gamma_2+\mu_1} & \frac{S_2^* m_{21}}{\gamma_2+\mu_2} & \frac{S_2^* m_{31}}{\gamma_2+\mu_3} & \frac{S_2^* m_{41}}{\gamma_2+\mu_4} & \frac{S_2^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_3^* m_{11}}{\gamma_2+\mu_1} & \frac{S_3^* m_{21}}{\gamma_2+\mu_2} & \frac{S_3^* m_{31}}{\gamma_2+\mu_3} & \frac{S_3^* m_{41}}{\gamma_2+\mu_4} & \frac{S_3^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_4^* m_{11}}{\gamma_2+\mu_1} & \frac{S_4^* m_{21}}{\gamma_2+\mu_2} & \frac{S_4^* m_{31}}{\gamma_2+\mu_3} & \frac{S_4^* m_{41}}{\gamma_2+\mu_4} & \frac{S_4^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_5^* m_{11}}{\gamma_2+\mu_1} & \frac{S_5^* m_{21}}{\gamma_2+\mu_2} & \frac{S_5^* m_{31}}{\gamma_2+\mu_3} & \frac{S_5^* m_{41}}{\gamma_2+\mu_4} & \frac{S_5^* m_{51}}{\gamma_2+\mu_5} \end{pmatrix} \tag{6.19}$$

The lower right 5×5 sub-matrix will be infectious age class j caused by infectious age class i. These will be similar to the upper right sub-matrix, but a proportion $(1-p)$ of infections result in infectious people. So the entries will be of the form: $\frac{\beta S_j^*(1-p)}{N(\gamma_2+\mu_i)} m_{ij}$.

$$D = \frac{\beta(1-p)}{N} \begin{pmatrix} \frac{S_1^* m_{11}}{\gamma_2+\mu_1} & \frac{S_1^* m_{21}}{\gamma_2+\mu_2} & \frac{S_1^* m_{31}}{\gamma_2+\mu_3} & \frac{S_1^* m_{41}}{\gamma_2+\mu_4} & \frac{S_1^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_2^* m_{11}}{\gamma_2+\mu_1} & \frac{S_2^* m_{21}}{\gamma_2+\mu_2} & \frac{S_2^* m_{31}}{\gamma_2+\mu_3} & \frac{S_2^* m_{41}}{\gamma_2+\mu_4} & \frac{S_2^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_3^* m_{11}}{\gamma_2+\mu_1} & \frac{S_3^* m_{21}}{\gamma_2+\mu_2} & \frac{S_3^* m_{31}}{\gamma_2+\mu_3} & \frac{S_3^* m_{41}}{\gamma_2+\mu_4} & \frac{S_3^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_4^* m_{11}}{\gamma_2+\mu_1} & \frac{S_4^* m_{21}}{\gamma_2+\mu_2} & \frac{S_4^* m_{31}}{\gamma_2+\mu_3} & \frac{S_4^* m_{41}}{\gamma_2+\mu_4} & \frac{S_4^* m_{51}}{\gamma_2+\mu_5} \\ \frac{S_5^* m_{11}}{\gamma_2+\mu_1} & \frac{S_5^* m_{21}}{\gamma_2+\mu_2} & \frac{S_5^* m_{31}}{\gamma_2+\mu_3} & \frac{S_5^* m_{41}}{\gamma_2+\mu_4} & \frac{S_5^* m_{51}}{\gamma_2+\mu_5} \end{pmatrix} \tag{6.20}$$

To simplify the matrices that take into account demographic change, we introduce κ_j^k be proportion of carriers in age class j who become a carrier in age class k. A carrier in age class j will become a carrier in age class $j+1$ at rate μ_j, and they remain carriers in age class j for an average $\frac{1}{\sigma+\gamma_1+\mu_j}$ years. From C_1 you can go on to any of the other C classes (as can be seen in Figure 6.8):

$$\begin{aligned} \kappa_1^2 &= \frac{\mu_1}{\sigma+\gamma_1+\mu_1} & \kappa_1^3 &= \kappa_1^2 \frac{\mu_2}{\sigma+\gamma_1+\mu_2} \\ \kappa_1^4 &= \kappa_1^3 \frac{\mu_3}{\sigma+\gamma_1+\mu_3} & \kappa_1^5 &= \kappa_1^4 \frac{\mu_4}{\sigma+\gamma_1+\mu_4} \end{aligned} \tag{6.21}$$

From C_2:

$$\begin{aligned} \kappa_2^3 &= \frac{\mu_2}{\sigma+\gamma_1+\mu_2} & \kappa_2^4 &= \kappa_2^3 \frac{\mu_3}{\sigma+\gamma_1+\mu_3} \\ \kappa_2^5 &= \kappa_2^4 \frac{\mu_4}{\sigma+\gamma_1+\mu_4} \end{aligned} \tag{6.22}$$

From C_3:

$$\kappa_3^4 = \frac{\mu_3}{\sigma+\gamma_1+\mu_3} \qquad \kappa_3^5 = \kappa_3^4 \frac{\mu_4}{\sigma+\gamma_1+\mu_4} \tag{6.23}$$

And from C_4 you can only go on to C_5:

$$\kappa_4^5 = \frac{\mu_4}{\sigma+\gamma_1+\mu_4} \tag{6.24}$$

The proportion of acutely infected age class j to become acutely infected age class k is given by η_j^k - from infected class j you move on to class $j+1$ at rate μ_j and remain

infectious for an average $\frac{1}{\gamma_2+\mu_j}$ years. From I_1 you can move through to be in any of the other I classes:

$$\begin{aligned} \eta_1^2 &= \frac{\mu_1}{\gamma_2+\mu_1} & \eta_1^3 &= \eta_1^2\frac{\mu_2}{\gamma_2+\mu_2} \\ \eta_1^4 &= \eta_1^3\frac{\mu_3}{\gamma_2+\mu_3} & \eta_1^5 &= \eta_1^4\frac{\mu_4}{\gamma_2+\mu_4} \end{aligned} \tag{6.25}$$

From I_2:

$$\begin{aligned} \eta_2^3 &= \frac{\mu_2}{\gamma_2+\mu_2} & \eta_2^4 &= \eta_2^3\frac{\mu_3}{\gamma_2+\mu_3} \\ \eta_2^5 &= \eta_2^4\frac{\mu_4}{\gamma_2+\mu_4} \end{aligned} \tag{6.26}$$

From I_3:

$$\eta_3^4 = \frac{\mu_3}{\gamma_2+\mu_3} \qquad \eta_3^5 = \eta_3^4\frac{\mu_4}{\gamma_2+\mu_4} \tag{6.27}$$

And from I_4:

$$\eta_4^5 = \frac{\mu_4}{\gamma_2+\mu_5} \tag{6.28}$$

We let ι_j^k be the proportion of carriers in age class j who become acutely infected in age class k. C_j become acutely infected at rate σ and remain carriers for an average $\frac{1}{\sigma+\gamma_1+\mu_j}$ years, from here they then become acutely infected class k (η_j^k), or from carrier class j they can become a carrier class k (κ_j^k) and then go on to be acutely infected. From C_1 to I_k:

$$\begin{aligned} \iota_1^1 &= \frac{\sigma}{\sigma+\gamma_1+\mu_1} \\ \iota_1^2 &= \iota_1^1\eta_1^2 + \kappa_1^2\frac{\sigma}{\sigma+\gamma_1+\mu_2} \\ \iota_1^3 &= \iota_1^2\eta_2^3 + \kappa_1^3\frac{\sigma}{\sigma+\gamma_1+\mu_3} \\ \iota_1^4 &= \iota_1^3\eta_3^4 + \kappa_1^4\frac{\sigma}{\sigma+\gamma_1+\mu_4} \\ \iota_1^5 &= \iota_1^4\eta_4^5 + \kappa_1^5\frac{\sigma}{\sigma+\gamma_1+\mu_5} \end{aligned} \tag{6.29}$$

From C_2 to I_k:

$$\begin{aligned} \iota_2^2 &= \frac{\sigma}{\sigma+\gamma_1+\mu_2} \\ \iota_2^3 &= \iota_2^2\eta_2^3 + \kappa_2^3\frac{\sigma}{\sigma+\gamma_1+\mu_3} \\ \iota_2^4 &= \iota_2^3\eta_3^4 + \kappa_2^4\frac{\sigma}{\sigma+\gamma_1+\mu_4} \\ \iota_2^5 &= \iota_2^4\eta_4^5 + \kappa_2^5\frac{\sigma}{\sigma+\gamma_1+\mu_5} \end{aligned} \tag{6.30}$$

From C_3 to I_k:

$$\begin{aligned}
\iota_3^3 &= \frac{\sigma}{\sigma+\gamma_1+\mu_3} \\
\iota_3^4 &= \iota_3^3\eta_3^4 + \kappa_3^4\frac{\sigma}{\sigma+\gamma_1+\mu_4} \\
\iota_3^5 &= \iota_3^4\eta_4^5 + \kappa_3^5\frac{\sigma}{\sigma+\gamma_1+\mu_5}
\end{aligned} \tag{6.31}$$

From C_4 to I_k:

$$\begin{aligned}
\iota_4^4 &= \frac{\sigma}{\sigma+\gamma_1+\mu_4} \\
\iota_4^5 &= \iota_4^4\eta_4^5 + \kappa_4^5\frac{\sigma}{\sigma+\gamma_1+\mu_5}
\end{aligned} \tag{6.32}$$

From C_5 to $I_5 = \iota_5^5 = \frac{\sigma}{\sigma+\gamma_2+\mu_5}$.

The matrix K^1 will represent the expected number of infections caused from carriers/acutely infected people after one change in age class. Columns 5 and 10 will contain zeros, as these represent infections caused by those initially carriers/acute infections in age class 5 – our last age class, so they can not move to another class. Column 1 will be infections caused by carriers who were initially in age class 1, but have since moved to age class 2, and may now be either carriers or acutely infected; similarly for columns 2 to 4. Column 6 will be infections caused by those who were initially acutely infected age class 1, and are now acutely infected age class 2; similarly for columns 7 to 9. We can split K^1 into four sub-matrices as shown below.

$$K^1 = \begin{pmatrix} A^1 & B^1 \\ C^1 & D^1 \end{pmatrix}$$

The sub-matrix A^1 represents the number of carriers caused by carriers who have moved up an age class. A proportion of carriers in age class j will create other carriers by either directly moving age classes in the carrier compartment (a proportion κ_j^{j+1}), or by becoming an acutely infected individual in age class $j+1$ (a proportion ι_j^{j+1}). Carriers in age class $j+1$ infect others at rate $\alpha\beta$, and remain carriers for an average $\frac{1}{\sigma+\gamma_1+\mu_{j+1}}$ years. Acutely infected class $j+1$ infect others at rate β and remain infectious for an average $\frac{1}{\gamma_2+\mu_{j+1}}$ years. They mix with class j at rate $m_{i,j+1}$, and a proportion p will

become carriers - the entries $A^1_{i,j}$ are of the form: $\frac{\beta m_{i,j+1} S^*_i}{N}\left(\frac{\alpha\kappa_j^{j+1}}{\sigma+\gamma_1+\mu_{j+1}}+\frac{\iota_j^{j+1}}{\gamma_2+\mu_{j+1}}\right)$

$$A^1=\frac{p\beta}{N}\begin{pmatrix} m_{12}S^*_1\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{13}S^*_1\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{22}S^*_2\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{23}S^*_2\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{32}S^*_3\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{33}S^*_3\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{42}S^*_4\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{43}S^*_4\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{52}S^*_5\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{53}S^*_5\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \end{pmatrix}$$
$$\begin{pmatrix} m_{14}S^*_1\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{15}S^*_1\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{24}S^*_2\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{25}S^*_2\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{34}S^*_3\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{35}S^*_3\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{44}S^*_4\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{45}S^*_4\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{54}S^*_5\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{55}S^*_5\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \end{pmatrix} \tag{6.33}$$

The sub-matrix C^1 represents the expected number of secondary cases of acute infections caused by people who were initially carriers in age class j but are now infectious in age class $j+1$; the entries are similar to those of A^1 but a proportion $(1-p)$ of those infected become acutely infected.

$$C^1=\frac{(1-p)\beta}{N}\begin{pmatrix} m_{12}S^*_1\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{13}S^*_1\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{22}S^*_2\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{23}S^*_2\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{32}S^*_3\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{33}S^*_3\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{42}S^*_4\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{43}S^*_4\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \\ m_{52}S^*_5\left(\frac{\alpha\kappa_1^2}{\sigma+\gamma_1+\mu_2}+\frac{\iota_1^2}{\gamma_2+\mu_2}\right) & m_{53}S^*_5\left(\frac{\alpha\kappa_2^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_2^3}{\gamma_2+\mu_3}\right) \end{pmatrix}$$
$$\begin{pmatrix} m_{14}S^*_1\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{15}S^*_1\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{24}S^*_2\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{25}S^*_2\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{34}S^*_3\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{35}S^*_3\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{44}S^*_4\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{45}S^*_4\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \\ m_{54}S^*_5\left(\frac{\alpha\kappa_3^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_3^4}{\gamma_2+\mu_4}\right) & m_{55}S^*_5\left(\frac{\alpha\kappa_4^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_4^5}{\gamma_2+\mu_5}\right) & 0 \end{pmatrix} \tag{6.34}$$

The sub-matrix B^1 represents the expected number of secondary cases of carrier infection caused by an acutely infectious person initially in age class j but now in age class $j+1$. From the acutely infectious class, a person can only move up to the subsequent acutely infected age class, so we will again have the fifth column being all zero. A proportion, η_j^{j+1}, of acutely infected individuals in age class j moves into age class $j+1$. They then infect others at rate β, and remain infectious for an average $\frac{1}{\gamma_2+\mu_{j+1}}$ years. They mix with age class i at rate m_{ij} and a proportion p of those infected become carriers. Thus,

entries in the matrix B^1 have the form: $\frac{pS_i^*}{N}\frac{m_{ij}\eta_j^{j+1}}{\gamma_2+\mu_{j+1}}$

$$B^1 = \frac{p}{N}\begin{pmatrix} \frac{m_{12}S_1^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{13}S_1^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{14}S_1^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{14}S_1^*\eta 4_5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{22}S_2^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{23}S_2^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{24}S_2^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{24}S_2^*\eta_4^5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{32}S_3^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{33}S_3^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{34}S_3^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{34}S_3^*\eta_4^5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{42}S_4^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{43}S_4^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{44}S_4^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{44}S_4^*\eta_4^5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{52}S_5^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{53}S_5^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{54}S_5^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{54}S_5^*\eta_4^5}{\gamma_2+\mu_5} & 0 \end{pmatrix} \tag{6.35}$$

The sub-matrix D^1 represents the expected number of secondary cases of acute infection caused by an acutely infected age class j individual who is now an acutely infected age class $j+1$ individual. This will be similar to the matrix B^1, apart from a proportion $1-p$ becoming acutely infected.

$$D^1 = \frac{(1-p)}{N}\begin{pmatrix} \frac{m_{12}S_1^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{13}S_1^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{14}S_1^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{14}S_1^*\eta_4^5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{22}S_2^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{23}S_2^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{24}S_2^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{24}S_2^*\eta_4^5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{32}S_3^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{33}S_3^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{34}S_3^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{34}S_3^*\eta_4^5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{42}S_4^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{43}S_4^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{44}S_4^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{44}S_4^*\eta_4^5}{\gamma_2+\mu_5} & 0 \\ \frac{m_{52}S_5^*\eta_1^2}{\gamma_2+\mu_2} & \frac{m_{53}S_5^*\eta_2^3}{\gamma_2+\mu_3} & \frac{m_{54}S_5^*\eta_3^4}{\gamma_2+\mu_4} & \frac{m_{54}S_5^*\eta_4^5}{\gamma_2+\mu_5} & 0 \end{pmatrix} \tag{6.36}$$

We construct the matrix K^2 in which we consider new cases of infection caused after infectious people have moved up two age classes. All the entries in columns 4, 5, 9, and 10 are now zero.

$$K^2 = \begin{pmatrix} A^2 & B^2 \\ C^2 & D^2 \end{pmatrix} \tag{6.37}$$

The sub-matrix A^2 represents the expected number of carriers that will occur due to a single carrier that has moved up two age groups. A proportion, κ_j^{j+2}, of carriers in age class j will become a carrier in age class $j+2$, who will infect others at rate $\alpha\beta$ and remain infectious for an average of $\frac{1}{\sigma+\gamma_1+\mu_{j+2}}$ years. They mix with age class i at rate $m_{i,j+2}$ and a proportion p of those infected will become carriers. A proportion of carriers, ι_j^{j+2}, in age class j can also go on to become an acutely infected person in age class $j+2$, who then infects others at rate β and remains infectious for an average of $\frac{1}{\gamma_2+\mu_{j+2}}$ years. So the (i,j) entry of A^2 will be of the form: $\frac{\beta p m_{i,j+2}S_i^*}{N}\left(\frac{\alpha\kappa_j^{j+2}}{\sigma+\gamma_1+\mu_{j+2}}+\frac{\iota_j^{j+2}}{\gamma_2+\mu_{j+2}}\right)$.

$$A^2 = \frac{\beta p}{N}\begin{pmatrix} S_1^* m_{13}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_1^* m_{14}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_1^* m_{15}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_2^* m_{23}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_2^* m_{24}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_2^* m_{25}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_3^* m_{33}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_3^* m_{34}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_3^* m_{35}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_4^* m_{43}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_4^* m_{44}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_4^* m_{45}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_5^* m_{53}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_5^* m_{54}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_5^* m_{55}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \end{pmatrix} \tag{6.38}$$

The sub-matrix C^2 will be similar to A^2, apart from a proportion $1-p$ of those infected become acutely infected:

$$C^2 = \frac{\beta(1-p)}{N}\begin{pmatrix} S_1^* m_{13}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_1^* m_{14}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_1^* m_{15}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_2^* m_{23}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_2^* m_{24}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_2^* m_{25}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_3^* m_{33}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_3^* m_{34}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_3^* m_{35}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_4^* m_{43}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_4^* m_{44}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_4^* m_{45}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \\ S_5^* m_{53}\left(\frac{\alpha\kappa_1^3}{\sigma+\gamma_1+\mu_3}+\frac{\iota_1^3}{\gamma_2+\mu_3}\right) & S_5^* m_{54}\left(\frac{\alpha\kappa_2^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_2^4}{\gamma_2+\mu_4}\right) & S_5^* m_{55}\left(\frac{\alpha\kappa_3^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_3^5}{\gamma_2+\mu_5}\right) & 0 & 0 \end{pmatrix} \tag{6.39}$$

The two right hand side sub-matrices of K^2 represent the number of new infections caused by acutely infected people who have moved up two age classes. A proportion, η_j^{j+2}, of acutely infected people in age class j become acutely infected age class $j+2$. They then infect people in age class i at rate $m_{i,j+2}\beta$ and remain infectious for an average $\frac{1}{\gamma_2+\mu_{j+2}}$ years, a proportion p become carriers, and a proportion $1-p$ become acutely infected.

$$B^2 = \frac{p\beta}{N}\begin{pmatrix} \frac{S_1^* m_{13}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_1^* m_{14}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_1^* m_{15}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_2^* m_{23}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_2^* m_{24}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_2^* m_{25}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_3^* m_{33}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_3^* m_{34}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_3^* m_{35}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_4^* m_{43}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_4^* m_{44}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_4^* m_{45}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_5^* m_{53}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_5^* m_{54}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_5^* m_{55}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \end{pmatrix} \tag{6.40}$$

and

$$D^2 = \frac{(1-p)\beta}{N}\begin{pmatrix} \frac{S_1^* m_{13}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_1^* m_{14}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_1^* m_{15}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_2^* m_{23}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_2^* m_{24}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_2^* m_{25}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_3^* m_{33}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_3^* m_{34}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_3^* m_{35}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_4^* m_{43}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_4^* m_{44}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_4^* m_{45}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \\ \frac{S_5^* m_{53}\eta_1^3}{\gamma_2+\mu_3} & \frac{S_5^* m_{54}\eta_2^4}{\gamma_2+\mu_4} & \frac{S_5^* m_{55}\eta_3^5}{\gamma_2+\mu_5} & 0 & 0 \end{pmatrix} \tag{6.41}$$

We construct K^3 and K^4 in a similar manner.

$$K^3 = \begin{pmatrix} A^3 & B^3 \\ C^3 & D^3 \end{pmatrix} \tag{6.42}$$

where:

$$A^3 = \frac{\beta p}{N}\times \begin{pmatrix} S_1^* m_{14}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_1^* m_{14}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_2^* m_{24}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_2^* m_{25}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_3^* m_{34}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_3^* m_{35}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_4^* m_{44}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_4^* m_{45}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_5^* m_{54}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_5^* m_{55}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \end{pmatrix} \tag{6.43}$$

$$C^3 = \frac{\beta(1-p)}{N}\times \begin{pmatrix} S_1^* m_{14}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_1^* m_{14}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_2^* m_{24}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_2^* m_{25}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_3^* m_{34}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_3^* m_{35}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_4^* m_{44}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_4^* m_{45}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \\ S_5^* m_{54}\left(\frac{\alpha\kappa_1^4}{\sigma+\gamma_1+\mu_4}+\frac{\iota_1^4}{\gamma_2+\mu_4}\right) & S_5^* m_{55}\left(\frac{\alpha\kappa_2^5}{\sigma+\gamma_1+\mu_5}+\frac{\iota_2^5}{\gamma_2+\mu_5}\right) & 0 & 0 & 0 \end{pmatrix} \tag{6.44}$$

$$B^3 = \frac{p\beta}{N}\begin{pmatrix} \frac{S_1^* m_{14}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_1^* m_{15}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_2^* m_{24}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_2^* m_{25}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_3^* m_{34}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_3^* m_{35}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_4^* m_{44}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_4^* m_{45}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_5^* m_{54}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_5^* m_{55}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \end{pmatrix} \tag{6.45}$$

$$D^3 = \frac{(1-p)\beta}{N}\begin{pmatrix} \frac{S_1^* m_{14}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_1^* m_{15}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_2^* m_{24}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_2^* m_{25}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_3^* m_{34}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_3^* m_{35}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_4^* m_{44}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_4^* m_{45}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \\ \frac{S_5^* m_{54}\eta_1^4}{\gamma_2+\mu_4} & \frac{S_5^* m_{55}\eta_2^5}{\gamma_2+\mu_5} & 0 & 0 & 0 \end{pmatrix} \tag{6.46}$$

Finally,

$$K^4 = \begin{pmatrix} A^4 & B^4 \\ C^4 & D^4 \end{pmatrix} \tag{6.47}$$

where:

$$A^4 = \frac{\beta p}{N} \begin{pmatrix} S_1^* m_{15} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_2^* m_{25} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_3^* m_{35} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_4^* m_{45} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_5^* m_{55} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \end{pmatrix} \tag{6.48}$$

$$C^4 = \frac{\beta(1-p)}{N} \begin{pmatrix} S_1^* m_{15} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_2^* m_{25} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_3^* m_{35} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_4^* m_{45} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \\ S_5^* m_{55} \left(\frac{\alpha \kappa_1^5}{\sigma+\gamma_1+\mu_5} + \frac{\iota_1^5}{\gamma_2+\mu_5} \right) & 0 & 0 & 0 & 0 \end{pmatrix} \tag{6.49}$$

$$B^4 = \frac{p\beta}{N} \begin{pmatrix} \frac{S_1^* m_{15} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_2^* m_{25} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_3^* m_{35} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_4^* m_{45} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_5^* m_{55} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{6.50}$$

$$D^4 = \frac{(1-p)\beta}{N} \begin{pmatrix} \frac{S_1^* m_{15} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_2^* m_{25} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_3^* m_{35} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_4^* m_{45} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \\ \frac{S_5^* m_{55} \eta_1^5}{\gamma_2+\mu_5} & 0 & 0 & 0 & 0 \end{pmatrix} \tag{6.51}$$

We can then calculate the basic reproduction ratio by taking the largest eigenvalue of our next generation matrix $K = K^1 + K^2 + K^3 + K^4$ when the entire population is susceptible. We have shown numerically that the eigenvalues of the Jacobian at the infection free steady state are all negative when $R_0 < 1$, indicating that the trivial steady state is stable, and then the Jacobian has a positive eigenvalue when R_0 passes one meaning the steady state changes stability, as shown in Figure 6.9.

Results

Solving Equations (6.12)–(6.13) numerically, using the parameter values shown in Table 6.2, we find the number of acutely infected people and carriers at any time t. To compare this to the known data on the number of infections recorded, we need to calculate the

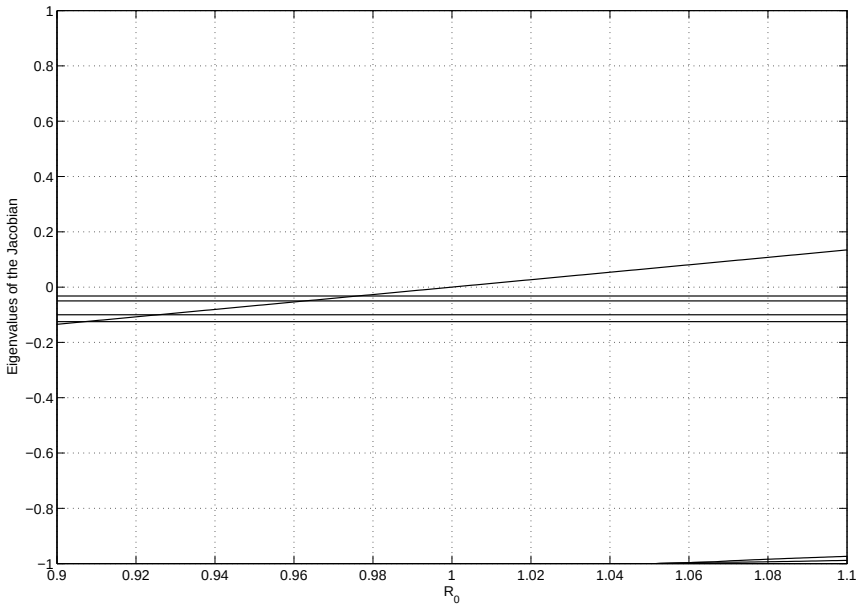


Figure 6.9: The larger eigenvalues of the Jacobian plotted again the basic reproduction ratio at the infection free steady state. The eigenvalues are all negative when $R_0 < 1$ indicating that the steady state is stable, but then R_0 increases above one, the trivial steady state becomes unstable as we have a positive eigenvalue from the Jacobian matrix.

incidence of infection (the number of new cases each year). The incidence of infection in age group j is given by:

$$i_j = (1-p)\lambda_j S_j + \sigma C_j \tag{6.52}$$

Thus, the incidence of infection each year is found by averaging the above equation over a one year time step. We can then compare this to the known data Kieft *et al.* (2001); Martin *et al.* (2007) (shown in Figure 6.10).

For this model, we have used an inter-age group mixing weight of $\epsilon = 0.4$ (in Equation (6.15)), with activity levels comparable to those used in Roberts & Tobias (2000) for modelling measles epidemics in New Zealand ($a_1 = 1$, $a_2 = 5$, $a_3 = 5$, $a_4 = 2$ and $a_5 = 1$).

The model results do not show a good fit to the data, especially in the older age classes where the model predicts much higher incidence of infection than actually seen, and under-predicts the number of cases in the infant age group. This may be due to the same parameter values being used for each age class - it is known that the probability of carriage decreases with age, and the incidence of infection also decreases with age. Therefore, to improve our model, we will introduce age dependent parameters.

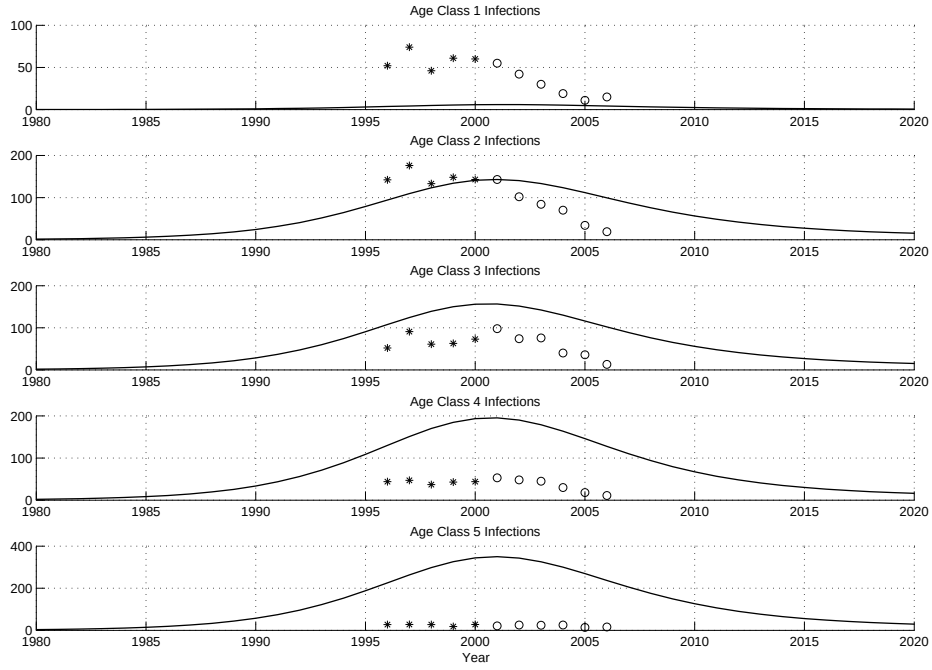


Figure 6.10: Yearly incidence of infection for the simple 5 age class model for meningococcal disease, showing the incidence in each age group. To start the epidemic pattern, one carrier in age class 4 was introduced into the population in 1960, with $R_0 = 1.15$. The stars are the recorded number of meningococcal infections in each year, and the circles are the recorded number of meningococcal serogroup B infections.

6.4.1 Five Age class model with age dependent parameters.

For this model we alter the parameters in each age class to allow for differences in the probability of becoming a carrier and being acutely infected, yet still follow a framework similar to the previous section. As we have seen in Chapter 4, for Hepatitis B virus the proportion of those infected who go on to become carriers is dependent on age, so we allow our parameter p to be different for each age class to see if that is also the case for meningococcal disease. We also let the parameter σ be different for each age class as a person's age may effect how quickly they recover from the invasive infection. The system of equations we solve is now:

$$\text{group 1 (0–1 years old)} \begin{cases} \frac{dS_1}{dt} = B - (\lambda_1 + \mu_1)S_1 \\ \frac{dC_1}{dt} = p_1\lambda_1 S_1 - (\sigma_1 + \gamma_1 + \mu_1)C_1 \\ \frac{dI_1}{dt} = (1-p_1)\lambda_1 S_1 + \sigma_1 C_1 - (\gamma_2 + \mu_1)I_1 \\ \frac{dR_1}{dt} = \gamma_1 C_1 + \gamma_2 I_1 - \mu_1 R_1 \end{cases} \tag{6.53}$$

$$\text{group 2 (1–10 years old)} \begin{cases} \frac{dS_2}{dt} = \mu_1 S_1 - (\lambda_2 + \mu_2)S_2 \\ \frac{dC_2}{dt} = \mu_1 C_1 + p_2\lambda_2 S_2 - (\sigma_2 + \gamma_1 + \mu_2)C_2 \\ \frac{dI_2}{dt} = \mu_1 I_1 + (1-p_2)\lambda_2 S_2 + \sigma_2 C_2 - (\gamma_2 + \mu_2)I_2 \\ \frac{dR_2}{dt} = \mu_1 R_1 + \gamma_1 C_2 + \gamma_2 I_2 - \mu_2 R_2 \end{cases} \tag{6.54}$$

$$\text{group 3 (10–20 years old)} \begin{cases} \frac{dS_3}{dt} = \mu_2 S_2 - (\lambda_3 + \mu_3)S_3 \\ \frac{dC_3}{dt} = \mu_2 C_2 + p_3\lambda_3 S_3 - (\sigma_3 + \gamma_1 + \mu_3)C_3 \\ \frac{dI_3}{dt} = \mu_2 I_2 + (1-p_3)\lambda_3 S_3 + \sigma_3 C_3 - (\gamma_2 + \mu_3)I_3 \\ \frac{dR_3}{dt} = \mu_2 R_2 + \gamma_1 C_3 + \gamma_2 I_3 - \mu_3 R_3 \end{cases} \tag{6.55}$$

$$\text{group 4 (20–40 years old)} \begin{cases} \frac{dS_4}{dt} = \mu_3 S_3 - (\lambda_4 + \mu_4)S_4 \\ \frac{dC_4}{dt} = \mu_3 C_3 + p_4\lambda_4 S_4 - (\sigma_4 + \gamma_1 + \mu_4)C_4 \\ \frac{dI_4}{dt} = \mu_3 I_3 + (1-p_4)\lambda_4 S_4 + \sigma_4 C_4 - (\gamma_2 + \mu_4)I_4 \\ \frac{dR_4}{dt} = \mu_3 R_3 + \gamma_1 C_4 + \gamma_2 I_4 - \mu_4 R_4 \end{cases} \tag{6.56}$$

$$\text{group 5 (40–70 years old)} \begin{cases} \frac{dS_5}{dt} = \mu_4 S_4 - (\lambda_5 + \mu_5)S_5 \\ \frac{dC_5}{dt} = \mu_4 C_4 + p_5\lambda_5 S_5 - (\sigma_5 + \gamma_1 + \mu_5)C_5 \\ \frac{dI_5}{dt} = \mu_4 I_4 + (1-p_5)\lambda_5 S_5 + \sigma_5 C_5 - (\gamma_2 + \mu_5)I_5 \\ \frac{dR_5}{dt} = \mu_4 R_4 + \gamma_1 C_5 + \gamma_2 I_5 - \mu_5 R_5 \end{cases} \tag{6.57}$$

We construct the next generation matrix in the same manner as for the last model (Equations (6.12)–(6.13)), but substitute for p_i and σ_i where appropriate. We then solve the system numerically, and find the incidence of infection so that we can compare it to known data - the results are shown in Figure 6.11. For this we used: $a_1 = 0.8$, $a_2 = 3$, $a_3 = 3.8$, $a_4 = 2$ and $a_5 = 1$ with $\epsilon = 0.4$; the infectivity of carriers relative to acutely

infected was $\alpha = 0.8$. We let the probability of becoming acutely infected from the carrier state and the rate of being acutely infected decrease with age: $p_1 = 0.96$, $p_2 = 0.9945$, $p_3 = 0.997$, $p_4 = 0.999$, and $p_5 = 0.9995$; and $\sigma_1 = 10^{-6}$ per year, $\sigma_2 = \sigma_3 = 10^{-7}$ per year, $\sigma_4 = \sigma_5 = 10^{-9}$ per year. Previously, in Equations (6.12)–(6.13), $p = 0.99$ and $\sigma = 0.0001$ for all age groups. The age dependant parameters model yields a closer fit to the data than the previous model, showing that there is a difference across the age groups in the probability of being infected. However, the time spent in each of the carrier compartments varies with age – which may not necessarily be true – we expect everyone to have a similar time as a carrier and acutely infected. The maximum time spent as a carrier is in age class 5, which is approximately half a year. Cartwright (1995); Trotter *et al.* (2006); Coen *et al.* (2000) estimate the duration of carriage to be an average of 10 months.

We have not included vaccination in our model yet, but the model already predicts a down turn in the total number of infections consistent with the data (on a total number of infections level, rather than age class level). The vaccination campaign was only started in 2004 – after the recorded and predicted number of acute infections was already decreasing. As there is little data available on the carriage rates of meningococcal disease or on how infective a carrier is relative to an acutely infected individual, this allows us some freedom in choosing our parameters to match the known data. However, it is possible for an individual to be in the carrier state more than once in their lifetime, so we now explore this possibility with models that include re-infection.

We have constructed a number of models so far that are based on the SCIR model, but none of these have given us a good fit to the known data. In the next chapter we shall explore different types of models to see if we can gain a better fit.

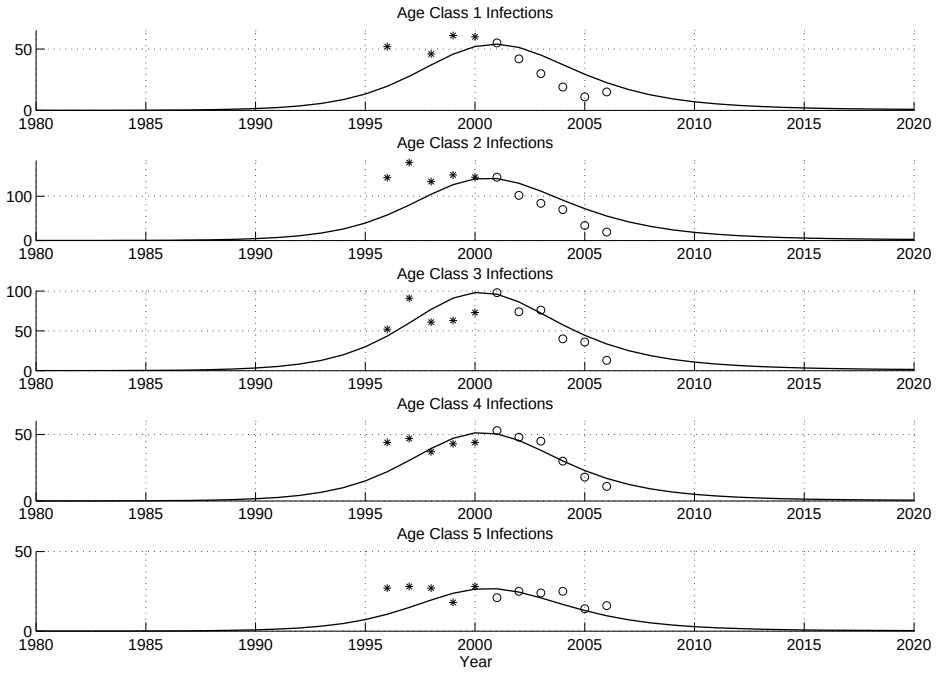


Figure 6.11: Numerical solution to the simple 5 age class model for meningococcal disease with age dependent proportions, showing the number of infected people in the population in each age group. To start the epidemic pattern, one carrier in each of age class 2 and age class 4 were introduced into the population in 1976, with $R_0 = 1.23$. The stars in are the recorded number of meningococcal infections in each year, and the circles are the recorded number of meningococcal serogroup B infections.

Chapter 7

Alternative Models for Meningococcal Disease in New Zealand

In the previous chapter, we have seen that a basic SCIR-type model can give us a close fit to the known yearly incidence of infection for meningococcal disease, but not what would be called a good fit. In this chapter, we shall explore some alternative models to see if we can gain a better fit to the data. By varying the structure of our model, we can investigate which mechanisms of the infection process play an important role in the spread of the infection.

7.1 Reinfection models, with no removed class.

We now include the possibility that a person can be in the carrier compartment multiple times in their lifetime (Cartwright (1995); Trotter & Gay (2003); Tyski *et al.* (2001)), and there is also a chance of developing the acute infection multiple times (although highly unlikely, as we have not found any strong supporting literature about this fact). From the susceptible age class, people can either become carriers or acutely infected; then from the carrier class, a small proportion will become acutely infected, or they may return to the susceptible class; from the acutely infected class, a person may return to the carrier class or to the susceptible class. There are a constant number of births into the susceptible population, and we allow the same death rate from each compartment. A schematic of this is shown in Figure 7.1.

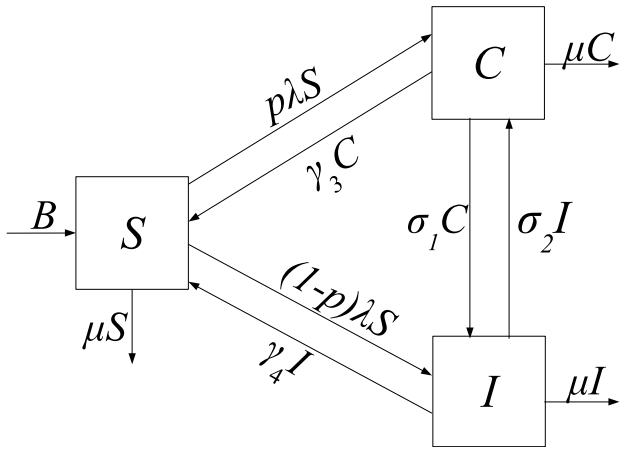


Figure 7.1: Flow diagram to depict the movement between compartments – susceptibles can become carriers or invasively infected; carriers can become susceptible again or invasively infected; and invasively infected people can become carriers or susceptible again. There is no immunity to infection, and a natural death rate from each compartment.

The system of equations for our new model is:

$$\begin{aligned}
\frac{dS}{dt} &= B - (\lambda + \mu)S + \gamma_3 C + \gamma_4 I \\
\frac{dC}{dt} &= p\lambda S + \sigma_2 I - (\sigma_1 + \gamma_3 + \mu)C \\
\frac{dI}{dt} &= (1-p)\lambda S + \sigma_1 C - (\gamma_4 + \sigma_2 + \mu)I
\end{aligned} \tag{7.1}$$

with

$$\begin{aligned}
\frac{dN}{dt} &= B - \mu N \\
\lambda &= \frac{\beta}{N}(I + \alpha C)
\end{aligned} \tag{7.2}$$

To calculate the next generation matrix, K, we decompose it as a sum of matrices $K = K^0 + K^1 + K^2 + ...$, where each superscript represents the number of changes in infectious type before infecting others. Initially, carriers infect others at rate $\alpha\beta$ and remain infectious for $\frac{1}{\mu+\sigma_1+\gamma_3}$ years. A proportion p of those infected will become carriers, while the proportion $(1-p)$ will go on to be acutely infected. Acutely infected people infect others at rate $\frac{\beta}{N}$ and remain infectious for an average $\frac{1}{\mu+\sigma_2+\gamma_4}$ years. When calculating the next generation matrix, we assume that the entire population is susceptible, so we multiple this by N. Thus, the first component of our next generation matrix is:

$$K^0 = \beta \begin{pmatrix} \frac{\alpha p}{\mu+\sigma_1+\gamma_3} & \frac{p}{\mu+\sigma_2+\gamma_4} \\ \frac{\alpha(1-p)}{\mu+\sigma_1+\gamma_3} & \frac{(1-p)}{\mu+\sigma_2+\gamma_4} \end{pmatrix} \tag{7.3}$$

A proportion of carriers become acutely infected $\frac{\sigma_1}{\mu+\sigma_1+\gamma_3}$, and a proportion of acutely

infected become carriers $\frac{\sigma_2}{\mu+\sigma_2+\gamma_4}$, both of whom then go on to infect others:

$$\begin{aligned} K^1 &= \beta \begin{pmatrix} \frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{p}{\mu+\sigma_2+\gamma_4} & \frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\alpha p}{\mu+\sigma_1+\gamma_3} \\ \frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{(1-p)}{\mu+\sigma_2+\gamma_4} & \frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\alpha(1-p)}{\mu+\sigma_1+\gamma_3} \end{pmatrix} \\ &= \frac{\beta}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)} \begin{pmatrix} \sigma_1 p & \sigma_2\alpha p \\ \sigma_1(1-p) & \sigma_2\alpha(1-p) \end{pmatrix} \end{aligned} \tag{7.4}$$

We now let there be two changes in infective class - a proportion of carriers go to be acutely infected then back to carriers, and a proportion of acutely infected go to carriers then back to acutely infected:

$$\begin{aligned} K^2 &= \beta \begin{pmatrix} \frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\alpha p}{\mu+\sigma_1+\gamma_3} & \frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{p}{\mu+\sigma_2+\gamma_4} \\ \frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\alpha(1-p)}{\mu+\sigma_1+\gamma_3} & \frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{(1-p)}{\mu+\sigma_2+\gamma_4} \end{pmatrix} \\ &= \frac{\beta\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)} \begin{pmatrix} \frac{\alpha p}{\mu+\sigma_1+\gamma_3} & \frac{p}{\mu+\sigma_2+\gamma_4} \\ \frac{\alpha(1-p)}{\mu+\sigma_1+\gamma_3} & \frac{(1-p)}{\mu+\sigma_2+\gamma_4} \end{pmatrix} \\ &= \frac{\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_3)} K^0 \end{aligned} \tag{7.5}$$

Progressing one stage further, our carriers become acutely infected and our acutely infected become carriers again:

$$\begin{aligned} K^3 &= \beta \begin{pmatrix} (\frac{\sigma_1}{\mu+\sigma_1+\gamma_3})^2\frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\alpha p}{\mu+\sigma_1+\gamma_3} & (\frac{\sigma_2}{\mu+\sigma_2+\gamma_4})^2\frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{p}{\mu+\sigma_2+\gamma_4} \\ (\frac{\sigma_1}{\mu+\sigma_1+\gamma_3})^2\frac{\sigma_2}{\mu+\sigma_2+\gamma_4}\frac{\alpha(1-p)}{\mu+\sigma_1+\gamma_3} & (\frac{\sigma_2}{\mu+\sigma_2+\gamma_4})^2\frac{\sigma_1}{\mu+\sigma_1+\gamma_3}\frac{(1-p)}{\mu+\sigma_2+\gamma_4} \end{pmatrix} \\ &= \frac{\beta\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)^2(\mu+\sigma_2+\gamma_4)^2} \begin{pmatrix} \sigma_1 p & \alpha\sigma_2 p \\ \sigma_1(1-p) & \alpha\sigma_2(1-p) \end{pmatrix} \\ &= \frac{\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)} K^1 \end{aligned} \tag{7.6}$$

From here we can see a pattern emerging, and it is easy to demonstrate:

$$\begin{aligned} K^4 &= \frac{\sigma_1^2\sigma_2^2}{(\mu+\sigma_1+\gamma_3)^2(\mu+\sigma_2+\gamma_4)^2} K^0 \\ K^5 &= \frac{\sigma_1^2\sigma_2^2}{(\mu+\sigma_1+\gamma_3)^2(\mu+\sigma_2+\gamma_4)^2} K^1 \\ K^6 &= \frac{\sigma_1^3\sigma_2^3}{(\mu+\sigma_1+\gamma_3)^3(\mu+\sigma_2+\gamma_4)^3} K^0 \\ K^7 &= \frac{\sigma_1^3\sigma_2^3}{(\mu+\sigma_1+\gamma_3)^3(\mu+\sigma_2+\gamma_4)^3} K^1 \end{aligned} \tag{7.7}$$

Summing these terms we get a series representation for our next generation matrix:

$$\begin{aligned}
K =& K^0 + K^1 + \frac{\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)}K^0 \\
&+ \frac{\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)}K^1 \\
&+ \frac{\sigma_1^2\sigma_2^2}{(\mu+\sigma_1+\gamma_3)^2(\mu+\sigma_2+\gamma_4)^2}K^0 \\
&+ \frac{\sigma_1^2\sigma_2^2}{(\mu+\sigma_1+\gamma_3)^2(\mu+\sigma_2+\gamma_4)^2}K^1 ... \\
=& (K^0+K^1)\left[1 + \frac{\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)}\right. \\
&\left. + \left(\frac{\sigma_1\sigma_2}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)}\right)^2 + ...\right]
\end{aligned} \tag{7.8}$$

The expression in the square brackets is a convergent geometric series, so our next generation matrix is:

$$\begin{aligned}
K =& (K^0+K^1)\frac{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)-\sigma_1\sigma_2} \\
=& \frac{\beta}{(\mu+\sigma_1+\gamma_3)(\mu+\sigma_2+\gamma_4)-\sigma_1\sigma_2}\times \\
& \begin{pmatrix} p(\alpha(\mu+\sigma_2+\gamma_4)+\sigma_1) & p(\alpha\sigma_2+(\mu+\sigma_1+\gamma_3)) \\ (1-p)(\alpha(\mu+\sigma_2+\gamma_4)+\sigma_1) & (1-p)(\alpha\sigma_2+(\mu+\sigma_1+\gamma_3)) \end{pmatrix}
\end{aligned} \tag{7.9}$$

The Jacobian matrix for Equations (7.1) is:

$$J = \begin{pmatrix} -(\lambda+\mu) & -\frac{\beta\alpha S}{N}+\gamma_3 & -\frac{\beta S}{N}+\gamma_4 \\ p\lambda & p\alpha\frac{\beta S}{N}-(\gamma_3+\sigma_1+\mu) & \frac{p\beta S}{N}+\sigma_2 \\ (1-p)\lambda & \frac{(1-p)\alpha\beta S}{N}+\sigma_1 & \frac{(1-p)\beta S}{N}-(\gamma_4+\sigma_2+\mu) \end{pmatrix}$$

We show numerically, Figure 7.2, that at the trivial steady state the Jacobian matrix has only negative eigenvalues (showing that the disease free state in stable) when $R_0 < 1$, and when $R_0 > 1$ a positive eigenvalue is found, so the disease free steady state becomes unstable.

Solving the system of Equations (7.1) numerically in Matlab, and plotting the incidence of acute infection with the known data (using the same method as in section 6.4), we see from Figure 7.3 that this model does not produce a very good fit. By introducing only one carrier in 1940, and having a very low value for the basic reproduction ratio ($R_0 = 1.16$), the number of people infected each year continues to climb until a very high endemic steady state is reached. The average time spent in the carriage state was 0.76 of a year, and in the acutely infected state was 0.1 of a year - which are realistic values. This model may not be a good fit as it does not include demographics, so our next step is to extend this model to our five age groups with age dependent probabilities of becoming acutely infected.

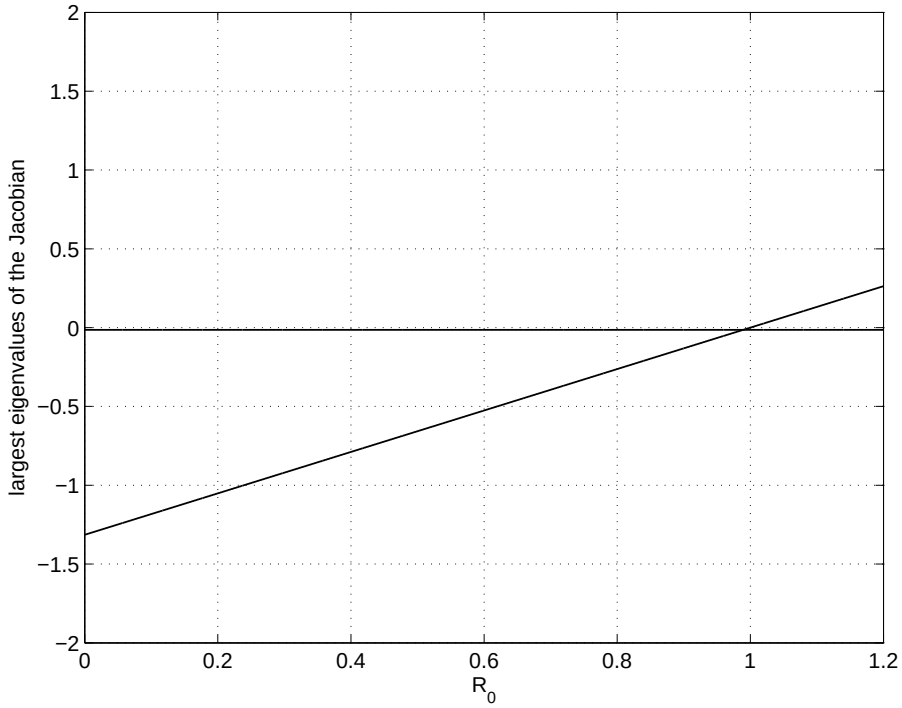


Figure 7.2: The largest eigenvalues of the Jacobian matrix versus R_0 at the disease free steady state. The Jacobian matrix has negative eigenvalues when $R_0 < 1$ indicating that the disease free steady state is stable, and when $R_0 > 1$ the Jacobian matrix has a positive eigenvalue indicating that the steady state is unstable.

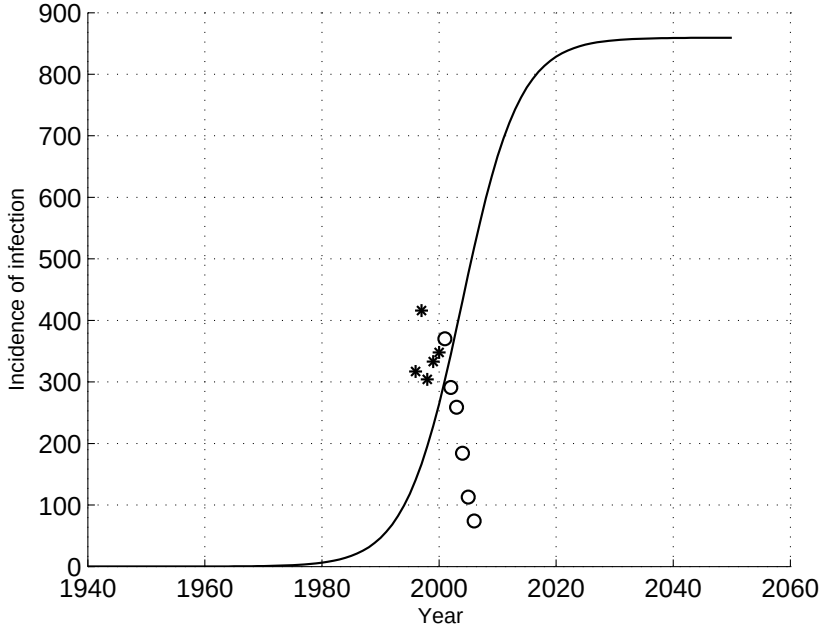


Figure 7.3: The yearly incidence of infection for the SCI reinfection model with the whole population as one age class. The epidemic was seeded with one carrier in 1940, and has $R_0 = 1.16$.

7.2 Five age class model with reinfection

We now split our population into five age groups and allow each age group to have an S, C and I compartment. Within each age group, people can move between the S, C and I compartments, but at the change of age group individuals can only move to the corresponding compartment in the next age class (e.g. from S_1 to S_2). The probability of becoming acutely infected is different for each age group, and we include the mixing matrix used previously (Equation (6.15)). Our system of equations is:

$$\text{group 1} \begin{cases} \frac{dS_1}{dt} = B - (\lambda_1 + \mu_1)S_1 + \gamma_3 C_1 + \gamma_4 I_1 \\ \frac{dC_1}{dt} = p_1\lambda_1 S_1 + \sigma_2 I_1 - (\sigma_1 + \gamma_3 + \mu_1)C_1 \\ \frac{dI_1}{dt} = (1-p_1)\lambda_1 S_1 + \sigma_1 C_1 - (\gamma_4 + \sigma_2 + \mu_1)I_1 \end{cases} \tag{7.10}$$

$$\text{groups 2–5} \begin{cases} \frac{dS_j}{dt} = \mu_{j-1}S_{j-1} - (\lambda_j + \mu_j)S_j + \gamma_3 C_j + \gamma_4 I_j \\ \frac{dC_j}{dt} = \mu_{j-1}C_{j-1} + p_j\lambda_j S_j + \sigma_2 I_j - (\sigma_1 + \gamma_3 + \mu_j)C_j \\ \frac{dI_j}{dt} = \mu_{j-1}I_{j-1} + (1-p_j)\lambda_j S_j + \sigma_1 C_j - (\gamma_4 + \sigma_2 + \mu_j)I_j \end{cases} \tag{7.11}$$

where

$$\lambda_i = \frac{\beta}{N}\sum_{k=1}^{5} m_{jk}(I_k + \alpha C_k) \tag{7.12}$$

To calculate the next generation matrix, we first consider a set of differential equations for the average amount of time spent in each of the infectious compartments ($\bar{C}_i$'s and $\bar{I}_i$'s):

$$\frac{d\bar{C}_j}{dt} = \sigma_2\bar{I}_j - (\gamma_3 + \sigma_1 + \mu_j)\bar{C}_j \quad \frac{d\bar{I}_j}{dt} = \sigma_1\bar{C}_j - (\gamma_4 + \sigma_2 + \mu_j)\bar{I}_j \tag{7.13}$$

for $j = 1 \ldots 5$. We can re-write this as a linear system in $\bar{C}_i$ and $\bar{I}_i$ such that:

$$\frac{d\mathbf{x}}{dt} = A\mathbf{x}, \quad \mathbf{x}(\mathbf{0}) = \mathbf{x_0} \tag{7.14}$$

the solution to which is $\mathbf{x}(t) = e^{At}\mathbf{x_0}$. We then calculate the expected time it takes to move between compartments, so we need $\int_0^\infty e^{At}\mathbf{x_0}dt$ for starting conditions in each compartment. It can be shown that the eigenvalues of A are all negative, so A is asymptotically stable, thus $\int_0^\infty e^{At}\mathbf{x_0}dt = -A^{-1}\mathbf{x_0}$, (Bernstein, 2005).

To find the expected amount of time that an individual from C_1 would take to get to each of the other infective compartments, we simply calculate $-A^{-1}\mathbf{e_1}$ (where $\mathbf{e_1}$ is the 1x10 vector with 1 in the first row and zeros everywhere else); the expected amount of time that an individual from C_2 would take to get to each of the other compartments is $-A^{-1}\mathbf{e_2}$, and so on for all the other compartments.

We let:

$$V = [-A^{-1}\mathbf{e_1}, -A^{-1}\mathbf{e_2}, -A^{-1}\mathbf{e_3}, \ldots, -A^{-1}\mathbf{e_{10}}] \tag{7.15}$$

Thus V is a 10×10 matrix, that gives us the number of sojourns an individual starting in any of the ten infectious compartments will take before reaching another infectious

compartment. We let M_2 be a matrix containing the mixing rates between age groups, and the expected number of people each type of infectious person is going to create:

$$M_2 = \frac{\beta}{N} \times \begin{bmatrix} S_1 p_1 \alpha m_{11} & \dots & S_1 p_1 \alpha m_{51} & S_1 p_1 m_{11} & \dots & S_1 p_1 m_{15} \\ S_2 p_2 \alpha m_{12} & \dots & S_2 p_2 \alpha m_{52} & S_2 p_2 m_{12} & \dots & S_2 p_2 m_{52} \\ S_3 p_3 \alpha m_{13} & \dots & S_3 p_3 \alpha m_{53} & S_3 p_3 m_{13} & \dots & S_3 p_3 m_{53} \\ S_4 p_4 \alpha m_{14} & \dots & S_4 p_4 \alpha m_{54} & S_4 p_4 m_{14} & \dots & S_4 p_4 m_{54} \\ S_5 p_5 \alpha m_{15} & \dots & S_5 p_5 \alpha m_{55} & S_5 p_5 m_{15} & \dots & S_5 p_5 m_{55} \\ S_1(1-p_1)\alpha m_{11} & \dots & S_1(1-p_1)\alpha m_{51} & S_1(1-p_1) m_{11} & \dots & S_1(1-p_1) m_{51} \\ S_2(1-p_2)\alpha m_{12} & \dots & S_2(1-p_2)\alpha m_{52} & S_2(1-p_2) m_{12} & \dots & S_2(1-p_2) m_{52} \\ S_3(1-p_3)\alpha m_{13} & \dots & S_3(1-p_3)\alpha m_{53} & S_3(1-p_3) m_{13} & \dots & S_3(1-p_3) m_{53} \\ S_4(1-p_4)\alpha m_{14} & \dots & S_4(1-p_4)\alpha m_{54} & S_4(1-p_4) m_{14} & \dots & S_4(1-p_4) m_{54} \\ S_5(1-p_5)\alpha m_{15} & \dots & S_5(1-p_5)\alpha m_{55} & S_5(1-p_5) m_{15} & \dots & S_5(1-p_5) m_{55} \end{bmatrix} \tag{7.16}$$

By multiplying the two matrices M_2 and V, we gain the next generation matrix, as this gives us the average number of new infections an individual from each compartment in every age group will make. The basic reproduction ratio is the largest eigenvalue of $K = M_2 V$. We can calculate numerically that the eigenvalues of the Jacobian are all negative when $R_0 < 1$ and cross through zero when $R_0 = 1$ at the disease free steady state, as shown in Figure 7.4.

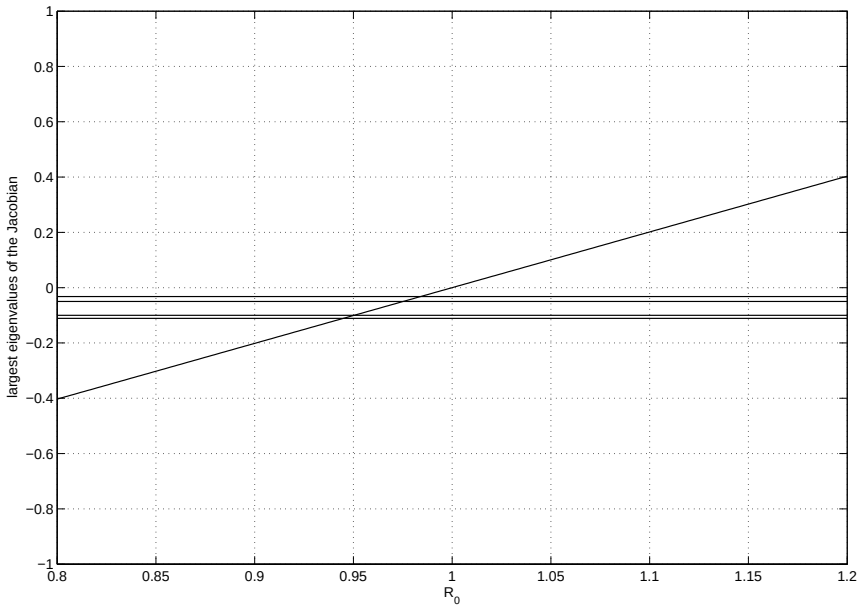


Figure 7.4: The top five eigenvalues of the Jacobian matrix plotted against the basic reproduction ratio at the disease free steady state for the five age class re-infection model.

Solving Equations (7.10)–(7.11) numerically and calculating the yearly incidence of infection (using the same method as in section 6.4), we gain the results shown in Figure 7.5. This simulation was seeded with one carrier in age class 4 in 1940 with a basic reproduction ratio of 1.1. Even with the probability of becoming acutely infected depending on age, and having non-homogeneous mixing between the age classes, this model still does not yield a good fit to the known data - our model approaches an endemic steady state rather than a peaked epidemic. As this model has not shown any relation to the data, we will not expand it to any more age classes. One reason for this type of model not being a good fit for meningococcal disease is that there is no time in which an individual in immune to infection, so our next step is to re-introduce a removed class to allow people to have immunity.

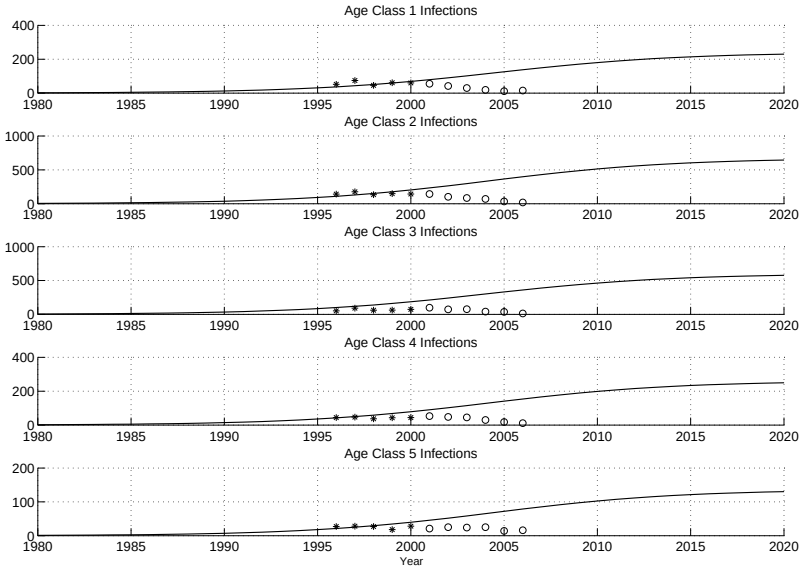


Figure 7.5: The number of people infected each year for the SCI reinfection model with the population split into age class. The epidemic was seeded with one carrier in age class 4 in 1940, and has $R_0 = 1.1$. Parameters used: $\alpha = 0.8$, $p_1 = 0.96$, $p_2 = 0.9945$, $p_3 = 0.997$, $p_4 = 0.999$, $p_5 = 0.9995$, $\sigma_1 = 10^{-5}$, $\sigma_2 = \sigma_1/100$, $\gamma_3 = 2$, $\gamma_4 = 10$; mixing parameters $a_1 = 0.8$, $a_2 = 3$, $a_3 = 3.8$, $a_4 = 2$, $a_5 = 1$ and $\epsilon = 0.4$.

7.3 Model with reinfection and immunity for acutely infected individuals.

We now consider a model where people can move back and forth between the carrier and susceptible compartments, but from the acutely infected compartment they can become immune to re-infection, as shown in Figure 7.6. From our previous model, we have let $\sigma_2 = \gamma_4 = 0$ to stop people who have been acutely infected begin infected again. We have done this as we have not found any documented cases of multiple infection with meningococcal B virus in New Zealand.

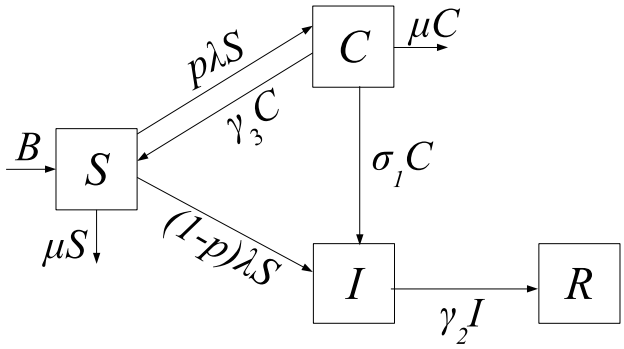


Figure 7.6: A model that allows individuals to be carriers multiple times, and allows there to be immunity to infection after being acutely infected.

Our system of equations is then:

$$\begin{aligned}
\frac{dS}{dt} &= B - (\lambda + \mu)S + \gamma_3 C \\
\frac{dC}{dt} &= p\lambda S - (\gamma_3 + \sigma_1 + \mu)C \\
\frac{dI}{dt} &= (1-p)\lambda S + \sigma_1 C - (\gamma_2 + \mu)I \\
\frac{dR}{dt} &= \gamma_2 I - \mu R
\end{aligned} \tag{7.17}$$

where

$$\lambda = \frac{\beta}{N}(I + \alpha C) \tag{7.18}$$

The next generation matrix is relatively straightforward to calculate for this model: Carriers remain infectious for an average $\frac{1}{\gamma_3+\sigma_1+\mu}$ years, and infect others at rate $\alpha\beta$. A proportion of carriers, $\frac{\sigma_1}{\gamma_3+\sigma_1+\mu}$, go on to become acutely infected, and infect others at rate β. A proportion p of those infected go on to be carriers, and a proportion $(1-p)$ go on to be acutely infected. Acutely infected people remain infectious for an average $\frac{1}{\gamma_2+\mu}$

years and infect others at rate β. So our next generation matrix is:

$$K = \begin{pmatrix} \frac{\beta p}{\mu+\sigma_1+\gamma_3}\left(\alpha + \frac{\sigma_1}{\gamma_2+\mu}\right) & \frac{\beta p}{\gamma_2+\mu} \\ \frac{\sigma_1}{\sigma_1+\gamma_3+\mu}\left(1 + \frac{\beta(1-p)}{\gamma_2+\mu}\right) + \frac{\alpha\beta(1-p)}{\gamma_2+\mu} & \frac{\beta(1-p)}{\gamma_2+\mu} \end{pmatrix}$$

The Jacobian matrix is:

$$J = \begin{pmatrix} -(\lambda+\mu) & -\frac{\alpha\beta S}{N} & -\frac{\beta S}{N} \\ p\lambda & \frac{p\alpha\beta S}{N} - (\gamma_3+\sigma_1+\mu) & \frac{p\beta S}{N} \\ (1-p)\lambda & \frac{\alpha\beta(1-p)S}{N} + \sigma_1 & \frac{(1-p)\beta S}{N} - (\gamma_2+\mu) \end{pmatrix}$$

We have shown numerically that when the basic reproduction ratio is less than one, the trivial steady is stable (as the Jacobian matrix has only negative eigenvalues). When $R_0 > 1$, the trivial steady state becomes unstable, as there exists a positive eigenvalue of the Jacobian matrix.

Solving this numerically, the results can be seen in Figure 7.7. The parameters used were: $\sigma = 10^{-5}$ per year, $\gamma_2 = 20$ per year, $\gamma_3 = 1.3$ per year, $\alpha = 0.8$, $p = 0.995$ and $\beta = 1.9$. The birth rate was kept fixed at 64,460 births per year. Again, this model does not yield a good fit to the data, as from introducing only one carrier in our population, the number of infections increases and plateaus to a high endemic level.

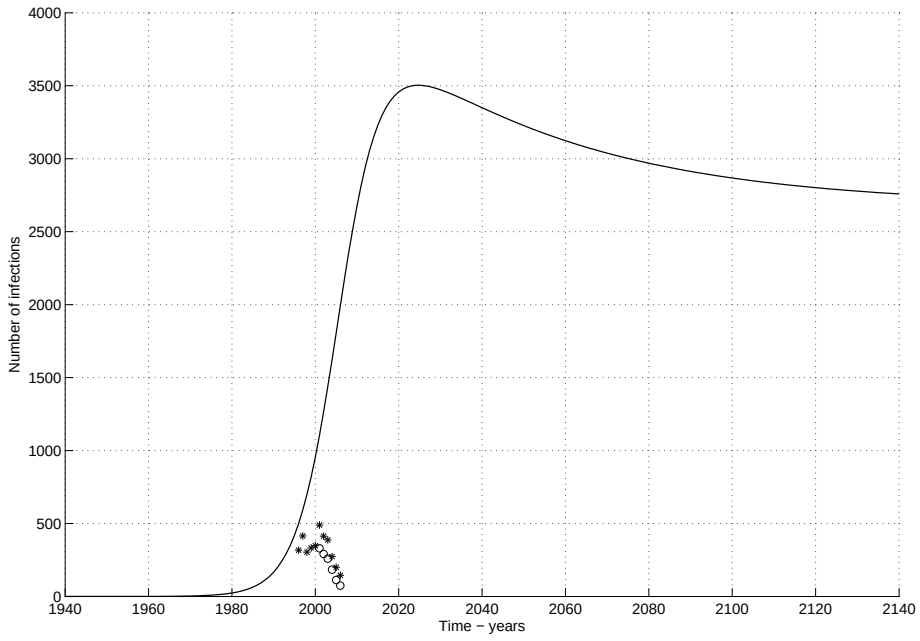


Figure 7.7: The yearly incidence of infection for the one age class model with reinfection possible into the carrier class, and immunity after being acutely infected. One carrier was introduced into the population in 1940, and the basic reproduction ratio was only 1.15.

As the past two models have not given us a good fit to the data, we discard the possibility of being able to be reinfected directly from the carrier class, and assume that there must be some time of immunity after being a carrier.

7.4 Temporary Immunity Model

We now return to an SCIR model, but with immunity only being temporary - from the removed compartment you may go back to the susceptible compartment. We consider the population as a whole, and then split this down into eight age classes.

Looking at the population as a whole, the equations for this model are:

$$\begin{aligned}\frac{dS}{dt} &= B - (\lambda + \mu)S + \gamma_3 R \\ \frac{dC}{dt} &= p\lambda S - (\sigma_1 + \gamma_1 + \mu)C \\ \frac{dI}{dt} &= (1-p)\lambda S + \sigma_1 C - (\gamma_2 + \mu)I \\ \frac{dR}{dt} &= \gamma_1 C + \gamma_2 I - (\mu + \gamma_3)R \end{aligned} \tag{7.19}$$

where

$$\lambda = \frac{\beta}{N}(I + \alpha C) \tag{7.20}$$

With the next generation matrix:

$$K = \begin{pmatrix} \frac{\beta p}{\sigma_1+\gamma_1+\mu}\left(\alpha + \frac{\sigma_1}{\gamma_2+\mu}\right) & \frac{\beta p}{\gamma_2+\mu} \\ \frac{1}{\sigma_1+\gamma_1+\mu}\left(\sigma_1 + \alpha\beta(1-p) + \frac{\sigma_1\beta(1-p)}{\gamma_2+\mu}\right) & \frac{\beta(1-p)}{\gamma_2+\mu} \end{pmatrix} \tag{7.21}$$

The Jacobian matrix is:

$$J = \begin{pmatrix} -(\lambda+\mu) & -\frac{\alpha\beta S}{N} & -\frac{\beta S}{N} \\ p\lambda & \frac{p\alpha\beta S}{N} - (\sigma_1+\gamma_1+\mu) & \frac{p\beta S}{N} \\ (1-p)\lambda & \frac{(1-p)\alpha\beta S}{N} + \sigma_1 & \frac{(1-p)\beta S}{N} - (\gamma_2+\mu) \end{pmatrix}$$

We have shown numerically that the eigenvalues of the Jacobian matrix are negative at the trivial steady state when $R_0 < 1$, and then become positive as R_0 increases above one. Thus the trivial steady state is stable when $R_0 < 1$ and becomes unstable when $R_0 > 1$.

Solving our equations numerically, and calculating the yearly incidence of infection, the results show a good fit to the known data, as shown in Figure 7.8. The parameters used for this solution are: $R_0 = 1.4$, $B = 64460$, $\mu = 1/70$, $\sigma_1 = 10^{-5}$, $\gamma_1 = 1.3$, $\gamma_2 = 10$, $\gamma_3 = 0.09$, $\alpha = 0.8$ and $p = 0.999$

The vaccination campaign was initiated in 2004, so we are concerned with matching the data for the years leading up to this. The yearly incidence of infection calculated from the results of our model should be lower than the total number of meningococcal disease

notification prior to 2001 as the recorded data was for all strains of meningococcal, not just strain B (shown as stars on the figure). Ideally our model should follow the number of strain B notifications (shown with a circle in Figure 7.8), or be a little above these to take into account the cases that were of the epidemic strain but could not be identified.

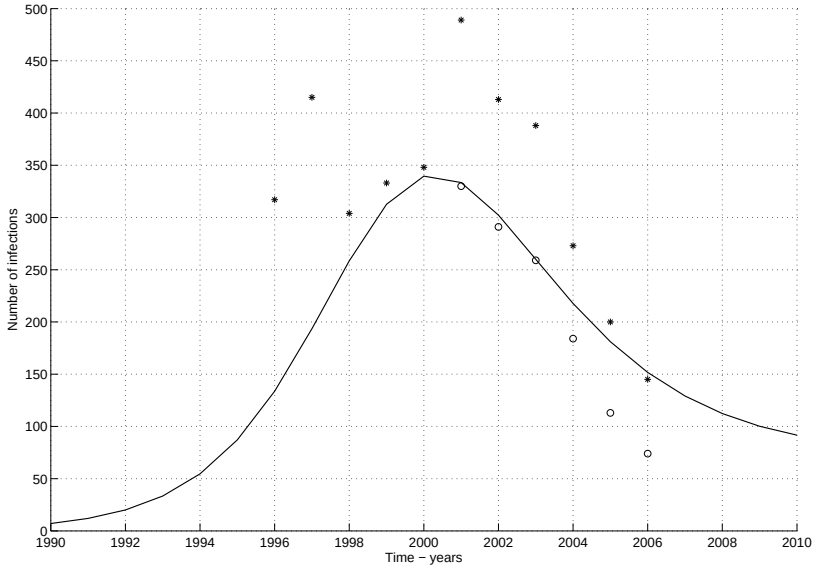


Figure 7.8: Numerical solution to the temporary immunity model for meningococcal disease, showing the yearly incidence of infection in the population. To start the epidemic pattern, one carrier was introduced into the population in 1975, with $R_0 = 1.4$. The stars are the recorded number of meningococcal infections in each year, and the circles are the recorded number of meningococcal serogroup B infections.

This model has produced a reasonable fit to the data, especially the strain B specific data between 2001–2004. Our model shows that the number of cases of infection were already decreasing before the vaccination campaign was launched, but would not have gone on to fall as low as the recorded number of infections with the effect of vaccination.

7.4.1 Temporary Immunity Model with population demographics

As the model for the population as a whole produced good results, we extend this to split our population into eight age classes to allow for different probabilities of developing the acute infection and of carriage (we have chosen eight age classes this time so that the results are easy to compare with known data, and the vaccination programme is easier to implement in the model). Our system of equations is now:

$$\text{group 1 (0–1 year old)} \begin{cases} \frac{dS_1}{dt} = B(t) - (\lambda_1 + \mu_1)S_1 + \gamma_3 R_1 \\ \frac{dC_1}{dt} = p_1\lambda_1 S_1 - (\sigma_1 + \gamma_1 + \mu_1)C_1 \\ \frac{dI_1}{dt} = (1-p_1)\lambda_1 S_1 + \sigma_1 C_1 - (\gamma_2 + \mu_1)I_1 \\ \frac{dR_1}{dt} = \gamma_1 C_1 + \gamma_2 I_1 - (\gamma_3 + \mu_1)R_1 \end{cases} \tag{7.22}$$

$$\text{group 2 (1–5 years old)} \begin{cases} \frac{dS_2}{dt} = \mu_1 S_1 + -(\lambda_2 + \mu_2)S_2 + \gamma_6 R_2 \\ \frac{dC_2}{dt} = \mu_1 C_1 + p_2\lambda_2 S_2 - (\sigma_2 + \gamma_4 + \mu_2)C_2 \\ \frac{dI_2}{dt} = \mu_1 I_1 + (1-p_2)\lambda_2 S_2 + \sigma_2 C_2 - (\gamma_5 + \mu_2)I_2 \\ \frac{dR_2}{dt} = \mu_1 R_1 + \gamma_4 C_2 + \gamma_5 I_2 - (\gamma_6 + \mu_2)R_2 \end{cases} \tag{7.23}$$

$$\text{group 3 (5–9 years old)} \begin{cases} \frac{dS_3}{dt} = \mu_2 S_2 - (\lambda_3 + \mu_3)S_3 + \gamma_9 R_3 \\ \frac{dC_3}{dt} = \mu_2 C_2 + p_3\lambda_3 S_3 - (\sigma_3 + \gamma_7 + \mu_3)C_3 \\ \frac{dI_3}{dt} = \mu_2 I_2 + (1-p_3)\lambda_3 S_3 + \sigma_3 C_3 - (\gamma_8 + \mu_3)I_3 \\ \frac{dR_3}{dt} = \mu_2 R_2 + \gamma_7 C_3 + \gamma_8 I_3 - (\gamma_9 + \mu_3)R_3 \end{cases} \tag{7.24}$$

$$\text{group 4 (9–12 years old)} \begin{cases} \frac{dS_4}{dt} = \mu_3 S_3 - (\lambda_4 + \mu_4)S_4 + \gamma_{12} R_4 \\ \frac{dC_4}{dt} = \mu_3 C_3 + p_4\lambda_4 S_4 - (\sigma_4 + \gamma_{10} + \mu_4)C_4 \\ \frac{dI_4}{dt} = \mu_3 I_3 + (1-p_1)\lambda_4 S_4 + \sigma_4 C_4 - (\gamma_{11} + \mu_4)I_4 \\ \frac{dR_4}{dt} = \mu_3 R_3 + \gamma_{10} C_4 + \gamma_{11} I_4 - (\gamma_{12} + \mu_4)R_4 \end{cases} \tag{7.25}$$

$$\text{group 5 (12–19 years old)} \begin{cases} \frac{dS_5}{dt} = \mu_4 S_4 - (\lambda_5 + \mu_5)S_5 + \gamma_{15} R_5 \\ \frac{dC_5}{dt} = \mu_4 C_4 + p_5\lambda_5 S_5 - (\sigma_5 + \gamma_{13} + \mu_5)C_5 \\ \frac{dI_5}{dt} = \mu_4 I_4 + (1-p_5)\lambda_5 S_5 + \sigma_5 C_5 - (\gamma_{14} + \mu_5)I_5 \\ \frac{dR_5}{dt} = \mu_4 R_4 + \gamma_{13} C_5 + \gamma_{14} I_5 - (\gamma_{15} + \mu_5)R_5 \end{cases} \tag{7.26}$$

$$\text{group 6 (19–25 years old)} \begin{cases} \frac{dS_6}{dt} = \mu_5 S_5 - (\lambda_6 + \mu_6)S_6 + \gamma_{18} R_6 \\ \frac{dC_6}{dt} = \mu_5 C_5 + p_6\lambda_6 S_6 - (\sigma_6 + \gamma_{16} + \mu_6)C_6 \\ \frac{dI_6}{dt} = \mu_5 I_5 + (1-p_6)\lambda_6 S_6 + \sigma_6 C_6 - (\gamma_{17} + \mu_6)I_6 \\ \frac{dR_6}{dt} = \mu_5 R_5 + \gamma_{16} C_6 + \gamma_{17} I_1 - (\gamma_{18} + \mu_6)R_6 \end{cases} \tag{7.27}$$

$$\text{group 7 (25–39 years old)} \begin{cases} \frac{dS_7}{dt} = \mu_6 S_6 - (\lambda_7 + \mu_7)S_7 + \gamma_{21} R_7 \\ \frac{dC_7}{dt} = \mu_6 C_6 + p_7 \lambda_7 S_7 - (\sigma_7 + \gamma_{19} + \mu_7)C_7 \\ \frac{dI_7}{dt} = \mu_6 I_6 + (1-p_7)\lambda_7 S_7 + \sigma_7 C_7 - (\gamma_{20} + \mu_7)I_7 \\ \frac{dR_7}{dt} = \mu_6 R_6 + \gamma_{19} C_7 + \gamma_{20} I_7 - (\gamma_{21} + \mu_7)R_7 \end{cases} \tag{7.28}$$

$$\text{group 8 (39–70 years old)} \begin{cases} \frac{dS_8}{dt} = \mu_7 S_7 - (\lambda_8 + \mu_8)S_8 + \gamma_{24} R_8 \\ \frac{dC_8}{dt} = \mu_7 C_7 + p_8 \lambda_8 S_8 - (\sigma_8 + \gamma_{22} + \mu_8)C_8 \\ \frac{dI_8}{dt} = \mu_7 I_7 + (1-p_8)\lambda_8 S_8 + \sigma_8 C_8 - (\gamma_{23} + \mu_8)I_8 \\ \frac{dR_8}{dt} = \mu_7 R_7 + \gamma_{22} C_8 + \gamma_{23} I_8 - (\gamma_{24} + \mu_8)R_8 \end{cases} \tag{7.29}$$

where

$$\lambda_i = \frac{\beta}{N} \sum_{k=1}^{8} m_{jk}(I_k + \alpha C_k) \tag{7.30}$$

We have used banded mixing rates and different weighting for inter-age class contacts for adults and children. The highest activity levels are for age classes 2–6 (one to nineteen years old), as they are most likely to take part in activities that would lead to the spread of the infection, i.e. children putting objects in their mouths at pre-school or teenagers sharing drink bottles. The mixing/contact matrix is:

$$M = \begin{pmatrix} a_1 & \epsilon\sqrt{a_1 a_2} & \epsilon\sqrt{a_1 a_3} & \epsilon_1\sqrt{a_1 a_4} \\ \epsilon_1\sqrt{a_2 a_1} & a_2 & \epsilon_1\sqrt{a_2 a_3} & \epsilon_1\sqrt{a_2 a_4} \\ \epsilon_1\sqrt{a_1 a_3} & \epsilon_1\sqrt{a_2 a_3} & a_3 & \epsilon_1\sqrt{a_3 a_4} \\ \epsilon_1\sqrt{a_1 a_4} & \epsilon_1\sqrt{a_4 a_2} & \epsilon_1\sqrt{a_4 a_3} & a_4 \\ \epsilon_1\sqrt{a_1 a_5} & \epsilon_1\sqrt{a_2 a_5} & \epsilon_1\sqrt{a_3 a_5} & \epsilon_1\sqrt{a_4 a_5} \\ \epsilon_1\sqrt{a_6 a_1} & \epsilon_1\sqrt{a_6 a_2} & \epsilon_1\sqrt{a_6 a_3} & \epsilon_1\sqrt{a_6 a_4} \\ \sqrt{\epsilon_1\epsilon_2}\sqrt{a_7 a_1} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_7 a_2} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_7 a_3} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_7 a_4} \\ \sqrt{\epsilon_1\epsilon_2}\sqrt{a_8 a_1} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_8 a_2} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_8 a_3} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_8 a_4} \end{pmatrix}$$

$$\begin{pmatrix} \epsilon_1\sqrt{a_1 a_5} & \epsilon_1\sqrt{a_1 a_6} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_1 a_7} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_1 a_8} \\ \epsilon_1\sqrt{a_2 a_5} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_2 a_6} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_2 a_7} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_2 a_8} \\ \epsilon_1\sqrt{a_3 a_5} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_3 a_6} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_3 a_7} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_3 a_8} \\ \epsilon_1\sqrt{a_4 a_5} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_4 a_6} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_4 a_7} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_4 a_8} \\ a_5 & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_5 a_6} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_5 a_7} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_5 a_8} \\ \epsilon_1\sqrt{a_6 a_5} & a_6 & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_6 a_7} & \sqrt{\epsilon_1\epsilon_2}\sqrt{a_6 a_8} \\ \sqrt{\epsilon_1\epsilon_2}\sqrt{a_7 a_5} & \epsilon_2\sqrt{a_7 a_6} & a_7 & \epsilon_2\sqrt{a_7 a_8} \\ \sqrt{\epsilon_1\epsilon_2}\sqrt{a_8 a_5} & \epsilon_2\sqrt{a_8 a_6} & \epsilon_2\sqrt{a_8 a_7} & a_8 \end{pmatrix} \tag{7.31}$$

The mixing parameters used are: $a_1 = 1$, $a_2 = 5$, $a_3 = 6$, $a_4 = 6$, $a_5 = 5$, $a_6 = 4$, $a_7 = 2$, $a_8 = 1$, $\epsilon_1 = 0.7$ and $\epsilon_2 = 0.5$.

To generate the next generation matrix, and hence the basic reproduction ratio, we use the matrix method for solving the set of differential equations for the acutely infectious and carrier compartments (as shown previously in section 7.3). The average times spent in

each of the carrier and acutely infected compartments are given by the following equations:

$$\begin{aligned}
\frac{d\bar{C}_1}{dt} &= -(\gamma_1+\sigma_1+\mu_1)\bar{C}_1 & \frac{d\bar{C}_5}{dt} &= \mu_4\bar{C}_4-(\gamma_{13}+\sigma_5+\mu_5)\bar{C}_5\\
\frac{d\bar{C}_2}{dt} &= \mu_1\bar{C}_1-(\gamma_4+\sigma_2+\mu_2)\bar{C}_2 & \frac{d\bar{C}_6}{dt} &= \mu_5\bar{C}_5-(\gamma_{16}+\sigma_6+\mu_6)\bar{C}_6\\
\frac{d\bar{C}_3}{dt} &= \mu_2\bar{C}_2-(\gamma_7+\sigma_3+\mu_3)\bar{C}_3 & \frac{d\bar{C}_7}{dt} &= \mu_6\bar{C}_6-(\gamma_{19}+\sigma_7+\mu_7)\bar{C}_7\\
\frac{d\bar{C}_4}{dt} &= \mu_3\bar{C}_3-(\gamma_{10}+\sigma_4+\mu_4)\bar{C}_4 & \frac{d\bar{C}_8}{dt} &= \mu_7\bar{C}_7-(\gamma_{22}+\sigma_8+\mu_8)\bar{C}_8
\end{aligned}$$

$$\begin{aligned}
\frac{d\bar{I}_1}{dt} &= \sigma_1\bar{C}_1-(\gamma_2+\mu_1)\bar{I}_1 & \frac{d\bar{I}_5}{dt} &= \mu_4\bar{I}_4+\sigma_5\bar{C}_5-(\gamma_{14}+\mu_5)\bar{I}_5\\
\frac{d\bar{I}_2}{dt} &= \mu_1\bar{I}_1+\sigma_2C_2-(\gamma_5+\mu_2)\bar{I}_2 & \frac{d\bar{I}_6}{dt} &= \mu_5\bar{I}_5+\sigma_6\bar{C}_6-(\gamma_{17}+\mu_6)\bar{I}_6\\
\frac{d\bar{I}_3}{dt} &= \mu_2\bar{I}_2+\sigma_3C_3-(\gamma_8+\mu_3)\bar{I}_3 & \frac{d\bar{I}_7}{dt} &= \mu_6\bar{I}_6+\sigma_7\bar{C}_7-(\gamma_{20}+\mu_7)\bar{I}_7\\
\frac{d\bar{I}_4}{dt} &= \mu_3\bar{I}_3+\sigma_4C_4-(\gamma_{11}+\mu_4)\bar{I}_4 & \frac{d\bar{I}_8}{dt} &= \mu_7\bar{I}_7+\sigma_8\bar{C}_8-(\gamma_{23}+\mu_8)\bar{I}_8
\end{aligned}$$

We can re-write this as a linear system in C_i and I_i such that: $\frac{d\mathbf{x}}{dt}=A\mathbf{x}$ with $\mathbf{x}(\mathbf{0})=\mathbf{x_0}$, where $\mathbf{x}$ is a vector representing each of the infectious classes. We can show that the matrix A is asymptotically stable, so we can integrate the solution to the matrix differential equation to give $-A^{-1}\mathbf{x_0}$. In the same way as in section (7.2) we generate the mixing/infectiousness matrix (M_2) (but using the mixing rates given above), and the matrix V containing the number of sojourns one person from each of the carrier/acutely infected compartments spends in all the other infectious compartments (the columns are generated from $-A^{-1}\mathbf{e_i}$), giving us our next generation matrix $K=M_2V$. We have verified numerically that the eigenvalues of the Jacobian matrix are all negative when the largest eigenvalue of the next generation matrix (R_0) is less than one, and the Jacobian matrix eigenvalues only become positive when R_0 passes unity.

We solve Equations (7.22)– (7.29) numerically in Matlab, using the parameters shown in Tables 7.1– 7.2. The birth rate was taken from recorded data (Statistics New Zealand, 2004), but letting $B(t)$ remain at 2007 numbers (64044) for subsequent years. From these numerical solutions, we calculate the incidence of infection in each age group to gain the results shown in Figures 7.9, 7.10 and 7.11. The values we use for each of the p_i parameters are all close to one, but the solution is very sensitive to changes in these parameters and it is the ones shown in Table 7.2 that gave us the best fit to the data. The parameters σ_i are close to zero, if we set these all to zero (hence stopping carriers from becoming acutely infected) the numerical results are not very different, but we have included it for a sense of completeness.

Our model slightly overestimates the yearly incidence of infection prior to 2000 (shown in Figure 7.10), but shows a good fit for the pre-vaccination data there after (2000–2004). The available data for the epidemic strain of meningococcal does not extend to the age class level (only total population), so when looking at our age class results (Figures 7.9) we can only compare our model to the reported number of all strains of meningococcal prior to 2001 and then the epidemic strain from 2001 until vaccination started (in 2004). Our aim is to have our model produce incidence numbers lower than the pre-2001 data, but as close as possible to the post 2001 data.

The parameters that we have used in our model give an average time of approximately 5.4 months spent in the carrier compartment (5.52 months for age classes 1–3, 5.4 months for age classes 4–6 and 5.28 months for age classes 7 and 8). Other estimates used have been as high as 13.3 months (Coen *et al.*, 2000). The expected number of days in the acutely infected compartment ranged from 2.59–3.61 (3.61 for age class 1, 3.65 for age class 2, 2.73 for age classes 3–6 and 2.59 for age classes 7 and 8).

We have a basic reproduction ratio of 1.27 for our model, we can also calculate the reproduction ratio at time t as the epidemic progresses, R_t. As the birth rate is changing over time, and the infection is never completely eliminated from the population, R_t will never rise to the initial value, R_0. Over time, the peaks in incidence rate and R_t decrease, and a steady state is reached where the disease is present and R_t is just above unity. Figure 7.12 shows the change in R_t as the epidemic progresses.

Death due to infection has not be included in this model, as there is a very low (3%) probability of death from the infection. We have performed the numerical solutions to the equations with this death rate included, and have not seen a noticible difference in the results, and so have not been included in this text.

From this model we can see that without vaccination the model predicts another epidemic with a peak of 219 cases of infection in 2034. However, the introduction of vaccination has already shown a decrease in the recorded incidence of infection with which our model does not coincide, so our next step is to include the affects of the vaccination campaign.

Parameter	Description	Value
μ_1	rate at which age class 1 people move to age class 2	1 per year
μ_2	rate at which age class 2 people move to age class 3	1/4 per year
μ_3	rate at which age class 3 people move to age class 4	1/4 per year
μ_4	rate at which age class 4 people move to age class 5	1/3 per year
μ_5	rate at which age class 5 people move to age class 6	1/7 per year
μ_6	rate at which age class 6 people move to age class 7	1/6 per year
μ_7	rate at which age class 7 people move to age class 8	1/14 per year
μ_8	rate that age class 8 are removed from our system	1/31 per year
σ_1	rate that carriers age class 1 become acutely infected	1×10^{-6} per year
σ_2	rate that carriers age class 2 become acutely infected	2×10^{-6} per year
σ_3	rate that carriers age class 3 become acutely infected	2×10^{-6} per year
σ_4	rate that carriers age class 4 become acutely infected	2×10^{-7} per year
σ_5	rate that carriers age class 5 become acutely infected	2×10^{-7} per year
σ_6	rate that carriers age class 6 become acutely infected	2×10^{-8} per year
σ_7	rate that carriers age class 7 become acutely infected	2×10^{-9} per year
σ_8	rate that carriers age class 8 become acutely infected	2×10^{-9} per year
p_1	proportion of infected age class 1 who go onto be carriers	0.955
p_2	proportion of infected age class 2 who go onto be carriers	0.99
p_3	proportion of infected age class 3 who go onto be carriers	0.996
p_4	proportion of infected age class 4 who go onto be carriers	0.995
p_5	proportion of infected age class 5 who go onto be carriers	0.997
p_6	proportion of infected age class 6 who go onto be carriers	0.997
p_7	proportion of infected age class 7 who go onto be carriers	0.9992
p_8	proportion of infected age class 8 who go onto be carriers	0.9992

Table 7.1: Description of parameters used in the eight age class model for the death rate, proportion of those infected that become carriers, and the rate for carriers becoming invasively infected for all the age classes.

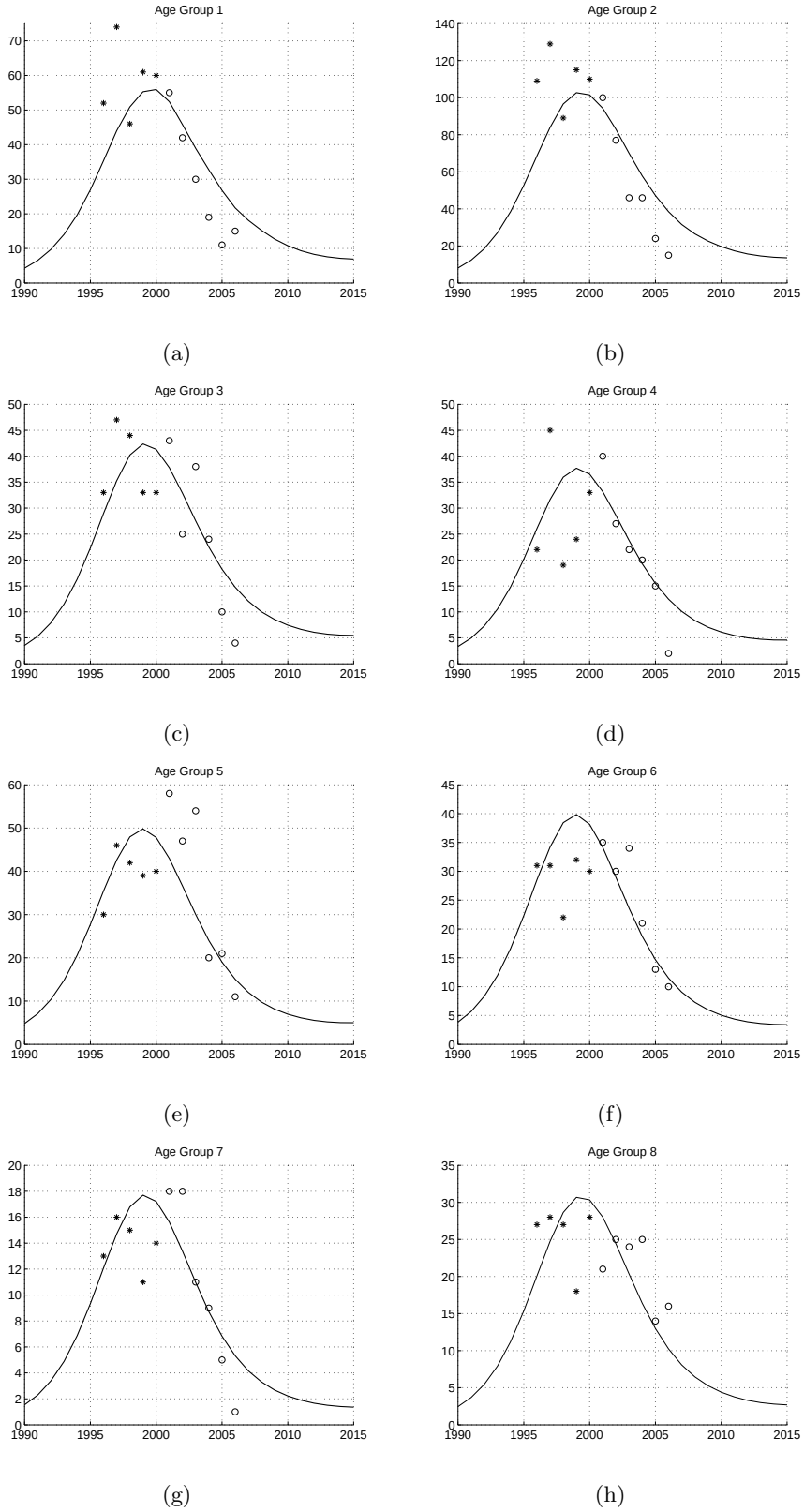


Figure 7.9: Numerical solution of the eight age class model with each age class shown individually. One carrier was introduced in age class five in 1974 to start the epidemic. Parameter values used are shown in Tables 7.1–7.2 and $R_0 = 1.27$.

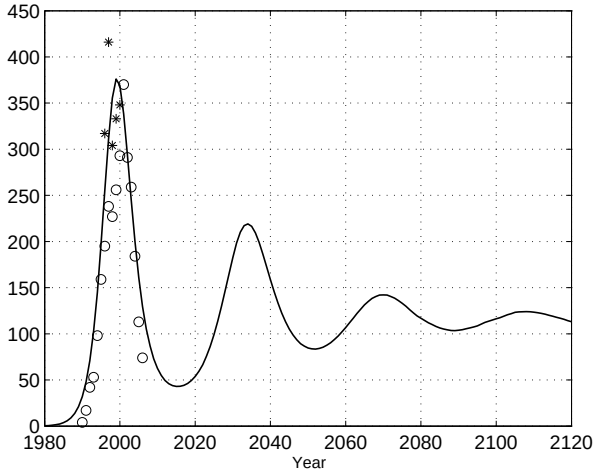


Figure 7.10: Numerical solution of the eight age class model for the years 1980–2120, with the total number of infections shown each year. One carrier introduced in age class five in 1974 to start the epidemic. Parameter values used are shown in Tables 7.1–7.2 and $R_0 = 1.27$.

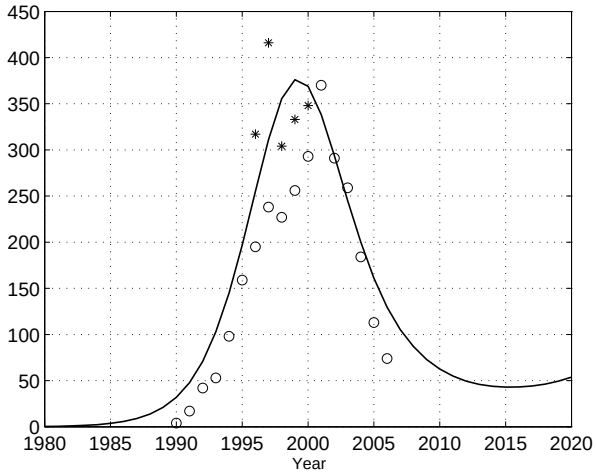


Figure 7.11: Numerical solution of the eight age class model for the years 1980–2020, with the total number of infections shown each year. One carrier introduced in age class five in 1974 to start the epidemic. Parameter values used are shown in Tables 7.1–7.2 and $R_0 = 1.27$.

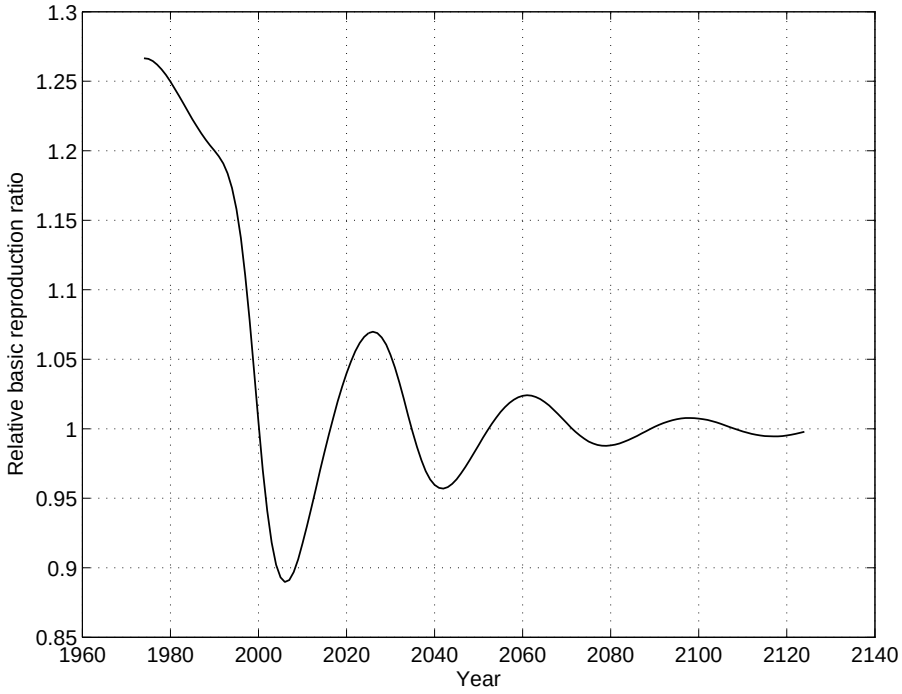


Figure 7.12: The effective reproduction ratio during the course of the epidemic for the eight age class model with no vaccination.

Parameter	Description	Value
γ_1	rate at which carriers become removed	1.1739 per year
γ_2	rate at which acutely infected become removed	100 per year
γ_3	rate at which removed become susceptible	0.05 per year
γ_4	rate at which carriers become removed	1.9239 per year
γ_5	rate at which acutely infected become removed	100 per year
γ_6	rate at which removed become susceptible	0.00425 per year
γ_7	rate at which carriers become removed	1.9239 per year
γ_8	rate at which acutely infected become removed	133.33 per year
γ_9	rate at which removed become susceptible	0.00283 per year
γ_{10}	rate at which carriers become removed	1.8889 per year
γ_{11}	rate at which acutely infected become removed	133.33 per year
γ_{12}	rate at which removed become susceptible	0.00283 per year
γ_{13}	rate at which carriers become removed	2.0796 per year
γ_{14}	rate at which acutely infected become removed	133.33 per year
γ_{15}	rate at which removed become susceptible	0.005 per year
γ_{16}	rate at which carriers become removed	2.0556 per year
γ_{17}	rate at which acutely infected become removed	133.33 per year
γ_{18}	rate at which removed become susceptible	0.005 per year
γ_{19}	rate at which carriers become removed	2.2013 per year
γ_{20}	rate at which acutely infected become removed	140 per year
γ_{21}	rate at which removed become susceptible	0.005 per year
γ_{22}	rate at which carriers become removed	2.2405 per year
γ_{23}	rate at which acutely infected become removed	140 per year
γ_{24}	rate at which removed become susceptible	0.00825 per year

Table 7.2: Description of parameters used in the eight age class model for the rates at which carriers and acutely infected individuals become removed, and removed individuals become susceptible again, for all age classes.

7.4.2 Temporary immunity model with demographics and vaccination.

We now add vaccination to our previous model by letting a proportion of each susceptible age class that is eligible for vaccination (under 20 year olds) move to the removed class. As the protection from vaccination is known to wane over time (Lennon, 2008), we incorporate this into our model with the movement of individuals from the removed class back to the susceptible class. We also include seasonal forcing, as disease incidence is notably higher in the winter/spring months (Martin *et al.*, 2007). Our system of equations is now:

$$\text{group 1 (0–1 year old)} \begin{cases} \frac{dS_1}{dt} = (1 - P_0(t))B(t) - (\lambda_1 + \mu_1)S_1 + \gamma_3 R_1 \\ \frac{dC_1}{dt} = p_1\lambda_1 S_1 - (\sigma_1 + \gamma_1 + \mu_1)C_1 \\ \frac{dI_1}{dt} = (1 - p_1)\lambda_1 S_1 + \sigma_1 C_1 - (\gamma_2 + \mu_1)I_1 \\ \frac{dR_1}{dt} = BP_0(t)\gamma_1 C_1 + \gamma_2 I_1 - (\gamma_3 + \mu_1)R_1 \end{cases} \tag{7.32}$$

$$\text{group 2 (1–5 years old)} \begin{cases} \frac{dS_2}{dt} = \mu_1 S_1(1 - P_1(t)) + -(\lambda_2 + \mu_2)S_2 + \gamma_6 R_2 \\ \frac{dC_2}{dt} = \mu_1 C_1 + p_2\lambda_2 S_2 - (\sigma_2 + \gamma_4 + \mu_2)C_2 \\ \frac{dI_2}{dt} = \mu_1 I_1 + (1 - p_2)\lambda_2 S_2 + \sigma_2 C_2 - (\gamma_5 + \mu_2)I_2 \\ \frac{dR_2}{dt} = \mu_1(R_1 + S_1 P_1(t)) + \gamma_4 C_2 + \gamma_5 I_2 - (\gamma_6 + \mu_2)R_2 \end{cases} \tag{7.33}$$

$$\text{group 3 (5–9 years old)} \begin{cases} \frac{dS_3}{dt} = \mu_2 S_2(1 - P_2(t)) - (\lambda_3 + \mu_3)S_3 + \gamma_9 R_3 \\ \frac{dC_3}{dt} = \mu_2 C_2 + p_3\lambda_3 S_3 - (\sigma_3 + \gamma_7 + \mu_3)C_3 \\ \frac{dI_3}{dt} = \mu_2 I_2 + (1 - p_3)\lambda_3 S_3 + \sigma_3 C_3 - (\gamma_8 + \mu_3)I_3 \\ \frac{dR_3}{dt} = \mu_2(R_2 + S_2 P_2(t)) + \gamma_7 C_3 + \gamma_8 I_3 - (\gamma_9 + \mu_3)R_3 \end{cases} \tag{7.34}$$

$$\text{group 4 (9–12 years old)} \begin{cases} \frac{dS_4}{dt} = \mu_3 S_3(1 - P_3(t)) - (\lambda_4 + \mu_4)S_4 + \gamma_{12} R_4 \\ \frac{dC_4}{dt} = \mu_3 C_3 + p_4\lambda_4 S_4 - (\sigma_4 + \gamma_{10} + \mu_4)C_4 \\ \frac{dI_4}{dt} = \mu_3 I_3 + (1 - p_1)\lambda_4 S_4 + \sigma_4 C_4 - (\gamma_{11} + \mu_4)I_4 \\ \frac{dR_4}{dt} = \mu_3(R_3 + S_3 P_3(t)) + \gamma_{10} C_4 + \gamma_{11} I_4 - (\gamma_{12} + \mu_4)R_4 \end{cases} \tag{7.35}$$

$$\text{group 5 (12–19 years old)} \begin{cases} \frac{dS_5}{dt} = \mu_4 S_4(1 - P_4(t)) - (\lambda_5 + \mu_5)S_5 + \gamma_{15} R_5 \\ \frac{dC_5}{dt} = \mu_4 C_4 + p_5\lambda_5 S_5 - (\sigma_5 + \gamma_{13} + \mu_5)C_5 \\ \frac{dI_5}{dt} = \mu_4 I_4 + (1 - p_5)\lambda_5 S_5 + \sigma_5 C_5 - (\gamma_{14} + \mu_5)I_5 \\ \frac{dR_5}{dt} = \mu_4(R_4 + S_4 P_4(t)) + \gamma_{13} C_5 + \gamma_{14} I_5 - (\gamma_{15} + \mu_5)R_5 \end{cases} \tag{7.36}$$

$$\text{group 6 (19–25 years old)} \begin{cases} \frac{dS_6}{dt} = \mu_5 S_5(1 - P_5(t)) - (\lambda_6 + \mu_6)S_6 + \gamma_{18}R_6 \\ \frac{dC_6}{dt} = \mu_5 C_5 + p_6\lambda_6 S_6 - (\sigma_6 + \gamma_{16} + \mu_6)C_6 \\ \frac{dI_6}{dt} = \mu_5 I_5 + (1 - p_6)\lambda_6 S_6 + \sigma_6 C_6 - (\gamma_{17} + \mu_6)I_6 \\ \frac{dR_6}{dt} = \mu_5(R_5 + S_5 P_5(t)) + \gamma_{16}C_6 + \gamma_{17}I_1 - (\gamma_{18} + \mu_6)R_6 \end{cases} \tag{7.37}$$

$$\text{group 7 (25–39 years old)} \begin{cases} \frac{dS_7}{dt} = \mu_6 S_6 - (\lambda_7 + \mu_7)S_7 + \gamma_{21}R_7 \\ \frac{dC_7}{dt} = \mu_6 C_6 + p_7\lambda_7 S_7 - (\sigma_7 + \gamma_{19} + \mu_7)C_7 \\ \frac{dI_7}{dt} = \mu_6 I_6 + (1 - p_7)\lambda_7 S_7 + \sigma_7 C_7 - (\gamma_{20} + \mu_7)I_7 \\ \frac{dR_7}{dt} = \mu_6 R_6 + \gamma_{19}C_7 + \gamma_{20}I_7 - (\gamma_{21} + \mu_7)R_7 \end{cases} \tag{7.38}$$

$$\text{group 8 (39–70 years old)} \begin{cases} \frac{dS_8}{dt} = \mu_7 S_7 - (\lambda_8 + \mu_8)S_8 + \gamma_{24}R_8 \\ \frac{dC_8}{dt} = \mu_7 C_7 + p_8\lambda_8 S_8 - (\sigma_8 + \gamma_{22} + \mu_8)C_8 \\ \frac{dI_8}{dt} = \mu_7 I_7 + (1 - p_8)\lambda_8 S_8 + \sigma_8 C_8 - (\gamma_{23} + \mu_8)I_8 \\ \frac{dR_8}{dt} = \mu_7 R_7 + \gamma_{22}C_8 + \gamma_{23}I_8 - (\gamma_{24} + \mu_8)R_8 \end{cases} \tag{7.39}$$

where

$$\lambda_i = \omega(t)\frac{\beta}{N}\sum_{k=1}^{8} m_{jk}(I_k + \alpha C_k) \tag{7.40}$$

$$\omega(t) = \begin{cases} (1+\delta)/(2\delta(\tau_2 - \tau_1) + 1 - \delta), \text{ if } \tau_1 < \tau < \tau_2 \\ (1-\delta)/(2\delta(\tau_2 - \tau_1) + 1 - \delta), \text{ otherwise} \end{cases} \tag{7.41}$$

where τ is the decimal part of t, and τ_1 is set to be the 1st July (0.5) and τ_2 is the first of September (0.67). So there is a lower transmission in the summer months than in the winter months. The mean value of ω is one, and for our numerical solutions we have used $\delta = 0.4$. This is the same seasonal forcing as used for modelling measles in New Zealand by Roberts & Tobias (2000).

The vaccination coverage rates are know from the National Immunisation Register, and we have used the coverage levels given in immunisation evaluation for the Ministry of Health (CBG Health Research Ltd, 2006). The effectiveness of vaccination was then varied to give our model the best fit to the known data. Vaccination was started in July 2004, and ended in June 2006, and we have assumed that all three doses are needed to give immunity.

$$P_0 = \begin{cases} 0.836 \times 0.73, \text{ if } 2004.4137 \le t < 2005.4137 \\ 0.47 \times 0.73, \text{ if } 2005.4137 \le t < 2006.4137 \end{cases}$$

$$P_1 = \begin{cases} 0.836 \times 0.73, \text{ if } 2004.4137 \le t < 2005.4137 \\ 0.82 \times 0.73, \text{ if } 2005.4137 \le t < 2006.4137 \end{cases}$$

$$P_2 = \begin{cases} 0.834 \times 0.73, \text{ if } 2004.4137 \leq t < 2005.4137 \\ 0.86 \times 0.73, \text{ if } 2005.4137 \leq t < 2006.4137 \end{cases}$$

$$P_3 = \begin{cases} 0.834 \times 0.73, \text{ if } 2004.4137 \leq t < 2005.4137 \\ 0.86 \times 0.73, \text{ if } 2005.4137 \leq t < 2006.4137 \end{cases}$$

$$P_4 = \begin{cases} 0.834 \times 0.73, \text{ if } 2004.4137 \leq t < 2005.4137 \\ 0.86 \times 0.73, \text{ if } 2005.4137 \leq t < 2006.4137 \end{cases}$$

$$P_5 = \begin{cases} 0.337 \times 0.73, \text{ if } 2004.4137 \leq t < 2005.4137 \\ 0.54 \times 0.73, \text{ if } 2005.4137 \leq t < 2006.4137 \end{cases} \tag{7.42}$$

The decimal parts of the time span numbers represents the 1st June each year. The 0.73 is the assumed efficacy of the vaccine, which is slightly lower than the estimated 80% efficacy given in Sexton *et al.* (2004). The coverage levels were taken from (CBG Health Research Ltd, 2006).

Solving the system of equations numerically and calculating the incidence of infection we can then compare our model to the recorded incidence of infection and the results from our previous model without vaccination, as shown in Figure 7.13–7.15. We can see that the model with vaccination shows a much better fit than our previous model to the data after vaccination was introduced, with our model passing through all the data points from 2001 when we look at the total incidence of infection. Figure 7.15 shows more of the long term trends of this epidemic - with the introduction of vaccination for two years the immediate incidence of infection was decreased well below what would have happened without vaccination. However, the model now predicts another epidemic, peaking with 324 cases in 2043, rather than a smaller peak (219 cases in 2034) if there had been no vaccination. The long term trend is for the incidence rate to settle to approximately 115 cases per year.

We can also look at some monthly data, as shown in Figure 7.16, where the solid line represents the monthly incidence in all age groups given from our model, and the dashed line with the stars is the monthly incidence of all strains of meningococcal disease (from literature). The seasonality in incidence of infection is not echoed in the number of carriers present in the population. As the data is for all strains of meningococcal disease, we want our model results to lie below these levels – they fail on this account in only three months over the six year period that the data are available. The fluctuations in incidence do not show on the graphs for yearly incidence, but it is interesting to see that there is a seasonality in the data.

We can also calculate the effect that vaccination has had on the effective reproduction ratio at time t, which we shall call R_{tv}, shown in Figure 7.17. Under vaccination, R_{tv} drops much lower than the reproduction ratio without vaccination, R_t, as expected. Yet,

in 2026 when R_t has reached its maximum, we see that R_{tv} is still increasing and reaches its peak in 2035. We see that for both cases (with and without the two year vaccination campaign), neither of the ratios go back to their initial level as the birth rate is changing over time, and the population is never fully susceptible to the infection again. As a result there is always some infection present.

Looking at how both R_t and R_{tv} change in relation to the incidence of infection, shown in Figure 7.18, we see that both ratios begin to decrease just prior to the epidemic peaks.

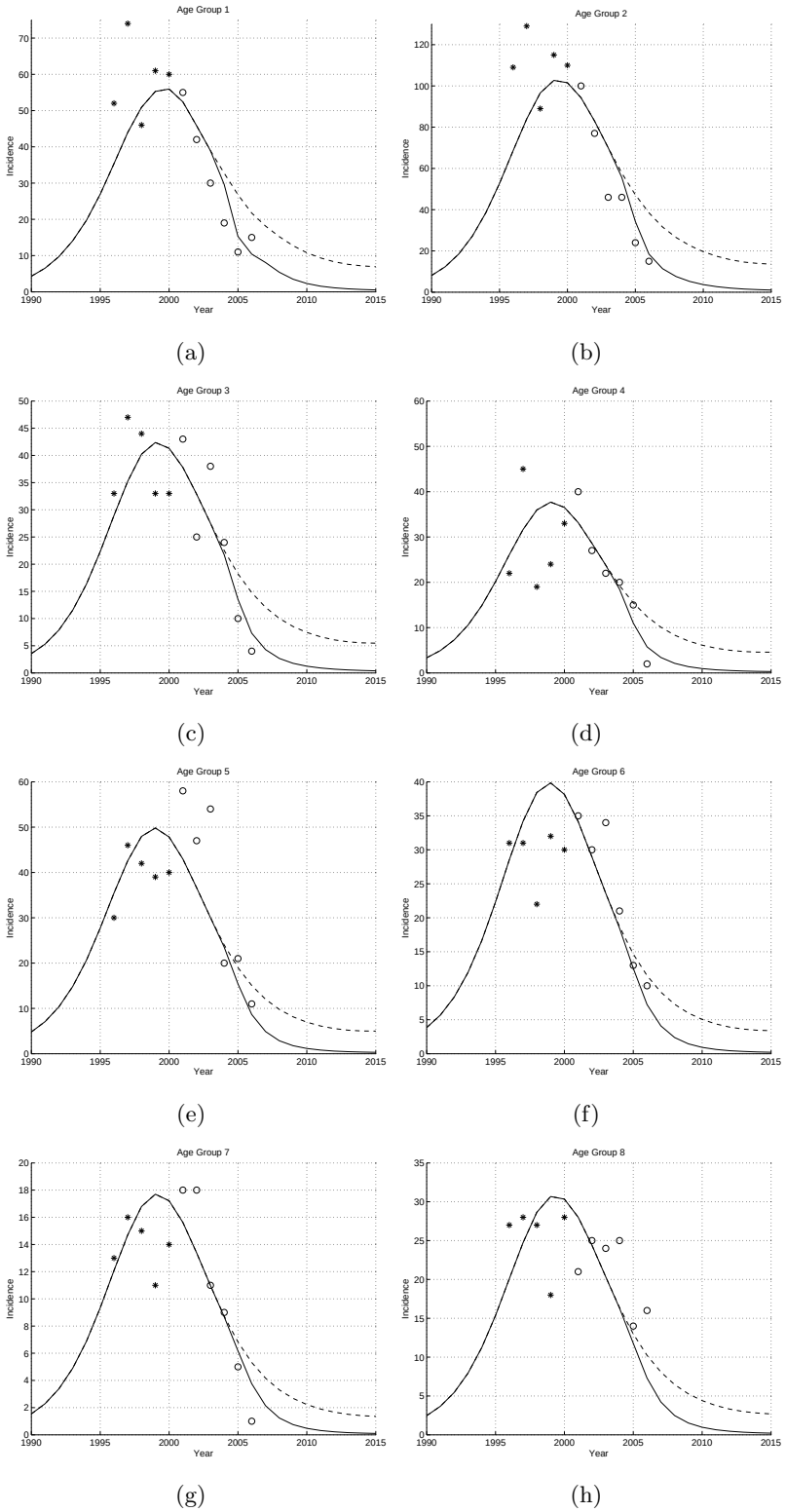


Figure 7.13: Numerical solution of the eight age class model with each age class with the current vaccination scheme shown individually. One carrier was introduced in age class five in 1974 to start the epidemic, and $R_0 = 1.27$. The dashed lines show the epidemic progress without vaccination, and the solid lines show the incidence when vaccination is included from 2004–2006.

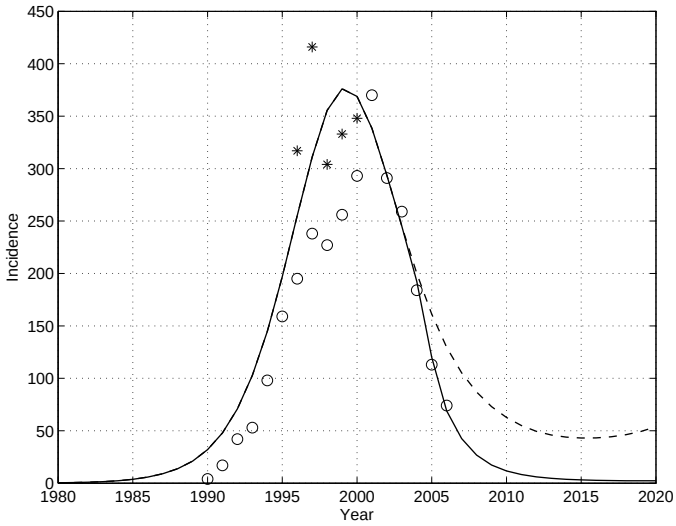


Figure 7.14: Numerical solution of the eight age class model from 1980–2020, with the total number of infections shown each year when vaccination is included (solid line). The dashed line is the incidence with no vaccination. One carrier introduced in age class five in 1974 to start the epidemic, and $R_0 = 1.27$.

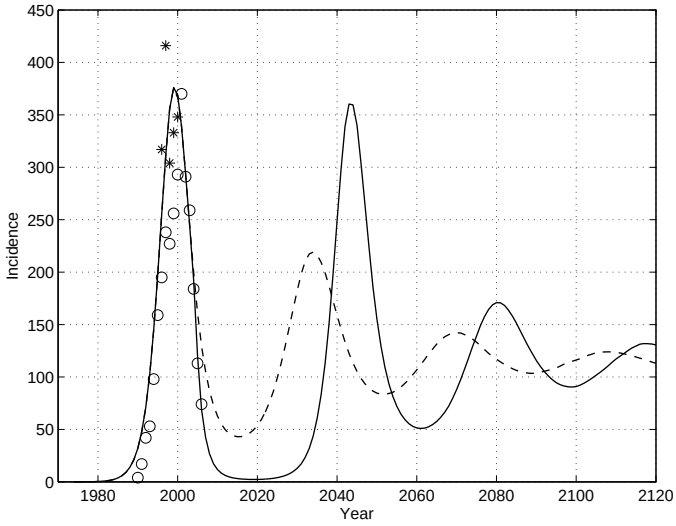


Figure 7.15: Numerical solution of the eight age class model from 1980–2120, with the total number of infections shown each year when vaccination is included (solid line). The dashed line is the incidence with no vaccination. One carrier introduced in age class five in 1974 to start the epidemic, and $R_0 = 1.27$.

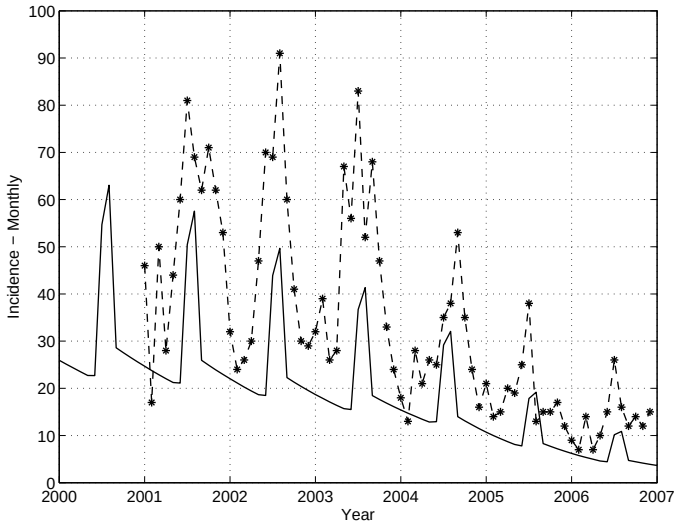


Figure 7.16: The monthly incidence of infection for the total population. The solid line is the model results, where the dashed line with the star represents the number of reported meningococcal disease cases (all strains).

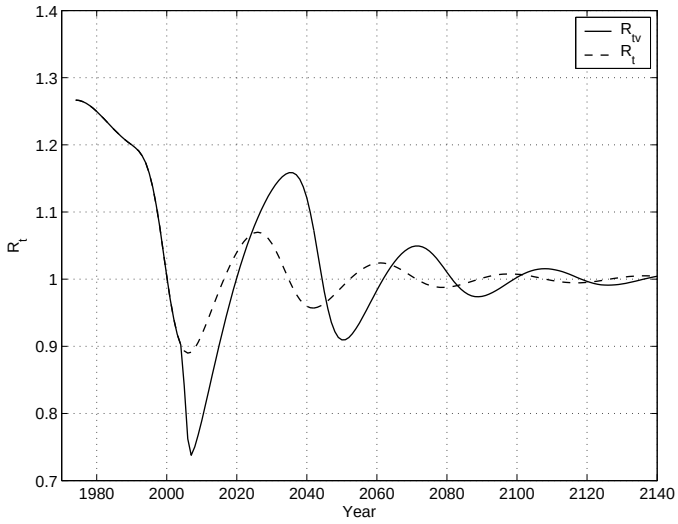
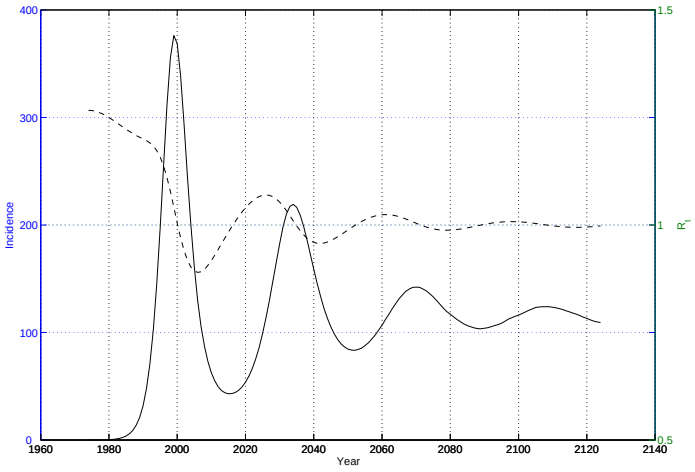
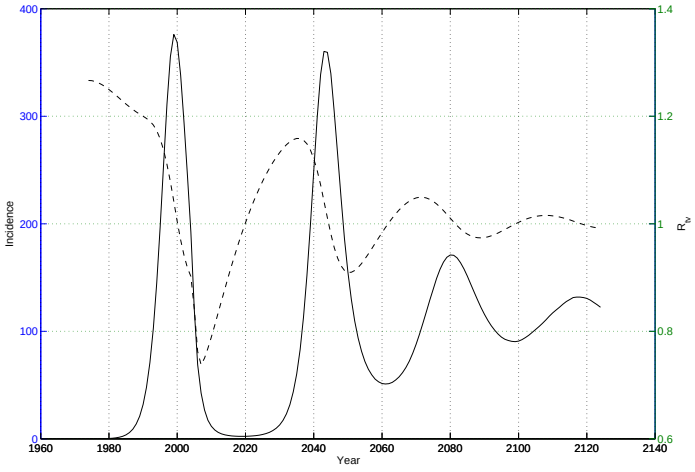


Figure 7.17: The dashed line is the effective reproduction ratio, R_t, and the solid line is the effective reproduction ratio under vaccination, R_{tv}. Initially, these are both equal to the basic reproduction ratio, $R_0 = 1.27$.



(a)



(b)

Figure 7.18: In both figures the solid line represents the incidence of infection and relates to the left hand scale, and the dashed line represents the effective reproduction ratio which relates to the right scale. Figure 7.18(a) shows the epidemic progress in the absence of vaccination, and Figure 7.18(b) shows the epidemic progress with the two years of vaccination included.

The effect of vaccination on the number of carriers.

From the solutions to Equations (7.32)–(7.39) we can calculate the yearly incidence of carriage in each class in a similar manner to calculating the yearly incidence of infection. The results of this are shown in Figures 7.19 and 7.20. Figure 7.19 shows the total incidence of carriage in the population. This is very similar in shape to the incidence of infection curve. As we saw for each of the age groups, the introduction of vaccination decreases the incidence of carriage initially, but it will then rise to a higher peak than would have been seen without vaccination. From Figure 7.20, we note that age class eight (39–70 years old) has the highest incidence, but as this is our largest age group that is not surprising. It can also be seen that the introduction of vaccination has decreased the incidence of carriage below what would have happened with no intervention, with the effect being seen immediately.

Figure 7.21 shows the total number of carriers in our population at any given time. The number of carriers is affected by the seasonality of infection, whereas the yearly incidence is not. From both of these figures (the yearly incidence and number of carriers), the long term trends for the vaccination and non-vaccination model have a similar result of the incidence/number settling to a steady state.

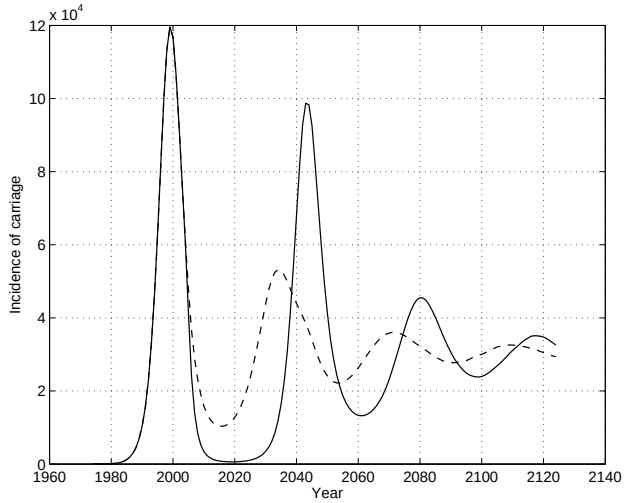


Figure 7.19: Numerical solution for the total incidence of carriage in the eight age class model with (solid line) and without (dashed line) the current vaccination scheme. One carrier was introduced in age class five in 1974 to start the epidemic, and $R_0 = 1.27$.

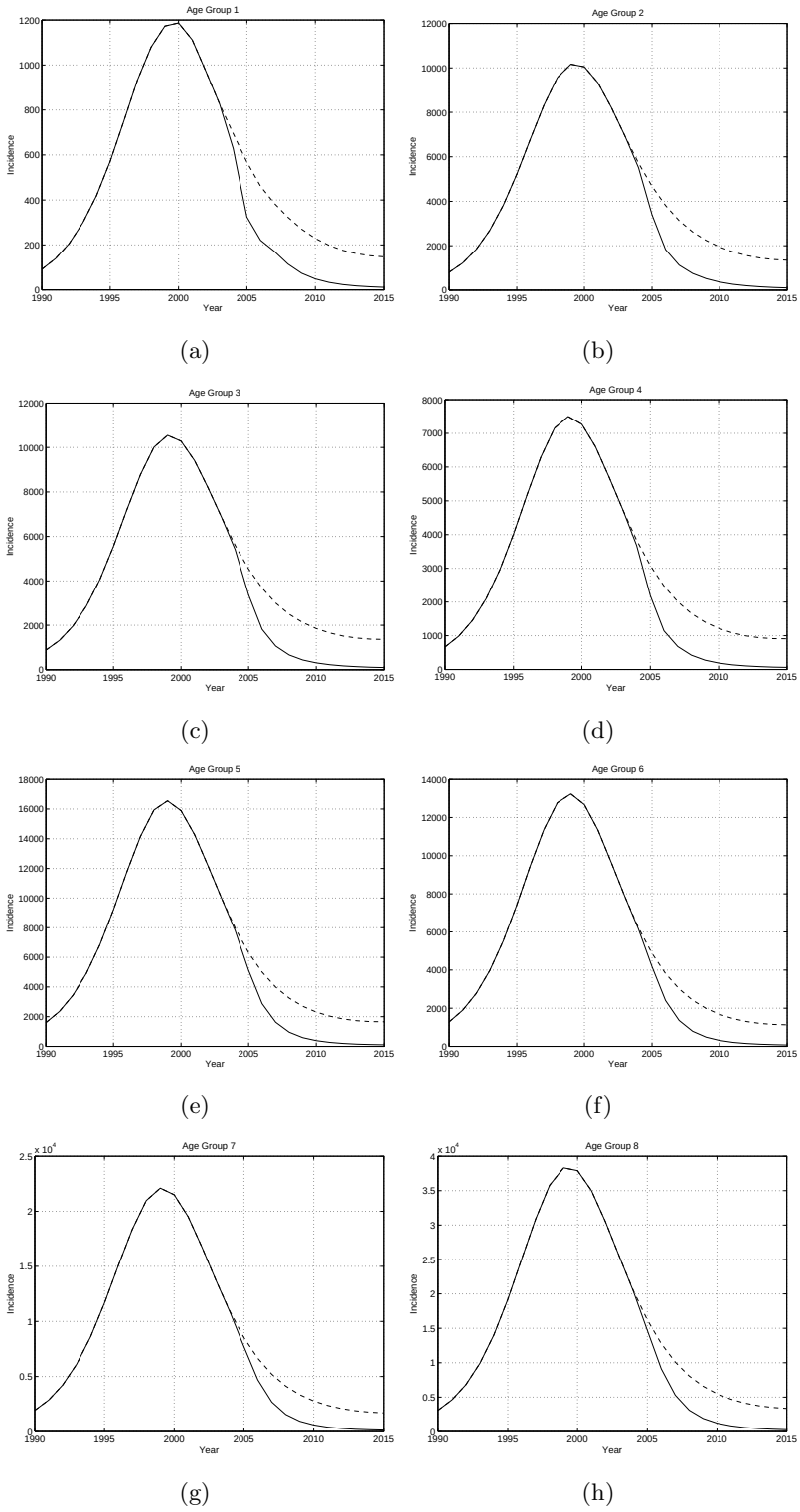


Figure 7.20: Numerical solution for the incidence of carriage in the eight age class model with each age class with the current vaccination scheme shown individually. One carrier was introduced in age class five in 1974 to start the epidemic, and $R_0 = 1.27$. The dashed lines show the epidemic progress without vaccination, and the solid lines show the incidence when vaccination is included from 2004–2006.

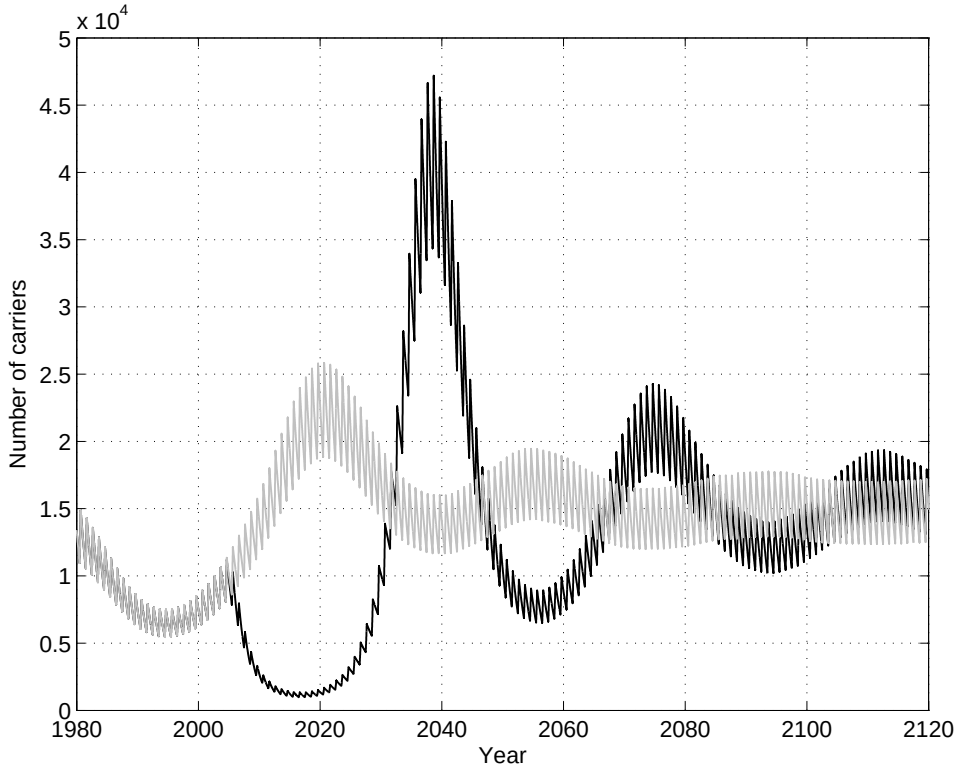


Figure 7.21: Numerical solution for the total number of carriers in the population for the eight age class model, with (dark line) and without (lighter grey line) the current vaccination scheme. Both lines zigzag within the year due to the seasonality of infection. One carrier was introduced in age class five in 1974 to start the epidemic, and $R_0 = 1.27$.

7.4.3 Exploring different vaccination schemes

Using our model from the previous section, we can now explore the effects that other possible vaccination schemes would have had on the epidemic. We shall consider thirteen different schemes, all implemented over the same two year period using the coverage rates and effectiveness for the vaccination programme that was implemented. These schemes are summarised in Table 7.3.

Scheme Symbol	Conditions
NV	No vaccination
CV	The current vaccination scheme of all under 20 year olds
V_0	Only vaccinating at birth (six weeks old)
V_1	Only vaccinating at one year old
V_5	Only vaccinating at five years old
V_9	Only vaccinating at nine years old
V_{12}	Only vaccinating at 12 years old
$V_{0,1}$	Vaccinating at birth and at one year old
$V_{1,5}$	Vaccinating at one year old and five years old
$V_{5,9}$	Vaccinating at five and nine years old
$V_{9,12}$	Vaccinating at nine and twelve years old
$V_{0,1,5}$	Vaccinating at birth, one year and five years old
$V_{0,1,5,9}$	Vaccinating at birth, one year, five years and nine years old
$V_{1,5,9}$	Vaccinating at one year, five years and nine years old
$V_{0,1,5,9,12}$	Vaccinating at birth, one year, five years, nine years, and twelve years old.

Table 7.3: The vaccination schemes that we used to explore the effect of vaccination on the incidence of infection and time until the next epidemic.

To compare the different schemes, we look at the lowest incidence of infection after the vaccination campaign (after 2006), and then at the highest incidence of infection for the next peak in the epidemic and when both of these occur. We calculated these values by altering our P_i values in Equations (7.32)–(7.39). The results are shown in Table 7.4. The vaccination schemes where only one age group is vaccinated (V_0, V_1, V_5, V_9 and V_{12}) do not have as great an effect as the ones where multiple age groups are vaccinated, yet they still bring the incidence of infection between epidemics significantly lower than with no vaccination. Vaccinating the first three ages groups – that is vaccinating at 6 weeks, 1 year and 5 years old – has the largest effect on the incidence of infection, as shown by vaccination schemes $V_{0,1,5}$, $V_{0,1,5,9}$, $V_{1,5,9}$ and $V_{0,5,9}$. Our last vaccination scheme (vaccinating everyone but the nineteen year olds) produced similar results to the campaign that was implemented, with the lowest number of cases after vaccination reaching 2.6 (compared to 2.3 with the current scheme), and the next epidemic peak occurring in 2043 with 355.2 cases (compared to a peak in the same year of 360.3 cases). The vaccination

scheme with only vaccinating those under twelve years old ($V_{0,1,5,9}$) also produced fairly low numbers, with the incidence dropping to 3.8 cases in 2018 then peaking again in 2042 with 345.6 cases. The vaccination schemes that only cover two age classes ($V_{0,1}$, $V_{1,5}$, $V_{5,9}$ and $V_{9,12}$) do not have as great an impact on the incidence as the schemes which cover more than two groups, however, with the two age group schemes the most improvement is seen from vaccination at one year and five years old.

Scheme Symbol	Lowest annual incidence after 2006 vaccination and year	Next peak incidence and year
NV	43, 2015	219, 2034
CV	3, 2018	361, 2043
V_0	23, 2016	287, 2036
V_1	20, 2017	269, 2037
V_5	23, 2015	260, 2035
V_9	28, 2016	247, 2035
V_{12}	31, 2016	241, 2035
$V_{0,1}$	13, 2017	293, 2038
$V_{1,5}$	11, 2017	301, 2039
$V_{5,9}$	15, 2016	286, 2037
$V_{9,12}$	21, 2016	266, 2036
$V_{0,1,5}$	7, 2018	326, 2040
$V_{0,1,5,9}$	4, 2018	346, 2042
$V_{1,5,9}$	7, 2018	326, 2040
$V_{0,1,5,9,12}$	3, 2018	356, 2043

Table 7.4: The results from the vaccination schemes specified in Table 7.3 – implemented using the same two year period for vaccination and vaccine effectiveness as in our previous model.

None of the vaccination schemes prevented a future epidemic, but they all altered the severity and timing of it. With the current vaccination scheme, our model predicts a future epidemic peaking in 2043 with 361 cases (compared to a peak in 2034 with 220 cases with no vaccination). The peak number of cases for a future epidemic increases as the number of cases after vaccination decreases. So the more effective a vaccination campaign is, the larger and sooner the future epidemic will be. The vaccination scheme $V_{0,1,5,9,12}$ that vaccinated at birth, one year, 5 years, 9 years and 12 years old gave us a low of 3 cases in 2018 and a peak of 356 cases in 2043 – which is comparable to the current scheme. This scheme would probably have been recommended, as it does not require the vaccination of teenagers who may have already left school and are therefore a significant coverage is harder to achieve.

As future epidemics are not eliminated by a two year vaccination campaign, vaccination is most likely going to have to be repeated. As launching a nation-wide vaccination

campaign is expensive and difficult, it would only be done when deemed necessary. The current vaccine had to be designed specifically for the New Zealand epidemic strain, which is what caused the delay in implementing the vaccination campaign, but it is now ready for future epidemics. Martin *et al.* (2007) deems an epidemic of meningococcal disease to be more than 50 cases of infection per year. If we wait for there to be 50 cases of infection (year 2035) before implementing a similar vaccination scheme (using the coverage levels and effectiveness from the previous section), we obtain the results shown in Figure 7.22. With a two year vaccination campaign, the immediate epidemic is avoided, but the incidence rate drops below fifty per year until 2051, when the same vaccination scheme could be implement to avoid the epidemic. As this is a new disease to New Zealand, the steady state has not yet been reached, so there will be fluctuating epidemics – yet these can be combated by vaccination.

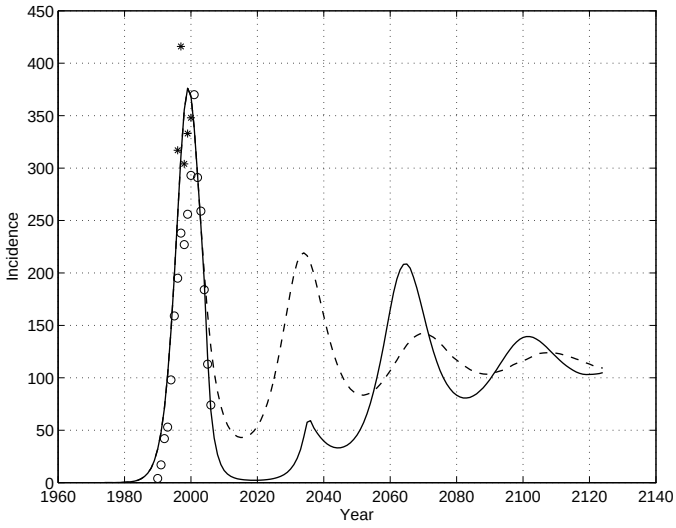


Figure 7.22: The solid line shows the model results for the eight age class meningococcal model with the vaccination included from 2004–2006 and then again in 2035–2037 at the same coverage rates and effectiveness. The dashed line shows the incidence of infection if there were no vaccination.

7.5 Discussion

We have presented various models for the incidence of infection of meningococcal disease in New Zealand, with the closest results to known data given by an SCIR model with feedback from the removed class to the susceptible class. Due to the nature of the disease, the models had to incorporate some form of demographics, with the younger age classes having a higher probability of being acutely infected. The alternative models presented in this chapter were included and motivated by the lack of fit to the know incidence numbers from our simple SCIR model in the previous chapter. As there are some unknown aspects to the spread of meningococcal disease (such as the infectiousness of carriers compared to

acutely infected individuals, and if a person is immune to reinfection for a limited amount of time), the alternative models presented in this chapter allowed us to explore different possibilities for the framework of the infection structure.

The reinfection models with no removed class, with and without population demographics, produced results where the incidence of infection increased steadily until an endemic steady state was reached. We think the main cause of this was the constant source of infection in the population, as there was no chance for immunity to be achieved thus allowing everyone to be infected multiple times. With the lack of immunity, there will always be infection in the population and we can not expect an epidemic to decline.

Our third model allowed there to be immunity for only those who had suffered from the acute form of infection. As the model showed a poor fit to the known data, we only looked at this model for the non-structured population. The fit to the data was poor, as again we had a large part of the population who were able to continuously spread the infection – as those who carried the infection could be re-infected multiple times, with little or no time in-between infections.

With the first four models results in mind, and the structured SCIR model presented in the previous chapter, a temporary immunity model was then considered. The ability to have immunity from infection after being a carrier or acutely infected allows the epidemic to peak and decline, as the epidemic in New Zealand has also shown. By including population demographics, and the affects of the vaccination campaign, we gained our best fitting model.

All our models are sensitive to the parameter values and the birth rates in terms of the incidence of infection and carriage. However, the general behaviour of each of seem robust to changes in the parameters, it is only the peak numbers of infections/carriers and the time-scale on which this happens that changes.

We have shown that the epidemic of meningococcal disease was already on the decline when the nation-wide vaccination campaign was launched. However, the introduction of the vaccine reduced the incidence of infection to a predicted low of three cases per year, compared to 43 per year with no vaccination. With such low numbers of infection, it would be possible for there to be stochastic fade out of the infection, meaning that small epidemics could occur as the infection gradually phases out of the population. The model also predicts future epidemics, yet these can be brought under control by another two year vaccination campaign similar to the one that has already been implemented.

Our final model required a relatively short duration of carriage compared to the estimated 9 to 10 months duration for American and European populations, and the lower 4.1 months for Nigeria (Cartwright, 1995). Our average duration of carriage is just over five months, which is slightly longer than the average three months carriage found by Trotter *et al.* (2005) when modelling the impact of the serogroup C vaccination in England and Wales. We assumed that vaccination gives complete protection against infection and carriage, whereas Trotter *et al.* (2005) let there be a small chance that there

could be carriage or infection after vaccination. Both our model and Trotter *et al.* (2005) assumed that the vaccination gave waning protection, in our model this was for the time that would be spent in the removed class (between 1 and 24 years depending on age) and in Trotter *et al.* (2005) protection lasted for an average of 15 months. The similarities in parameter estimates and results in our model and Trotter *et al.* (2005) are surprising, as they are two very differently structured models in terms of compartmentalising the state of a individual in relation to the disease. The United Kingdom routinely vaccinates infants against meningococcal C, and launched a nation-wide vaccination campaign in 1999 to vaccinate those under 25 who had not been vaccinated in the hope of ending their epidemic. Both our model and Trotter *et al.* (2005) predict that there will be future epidemics of meningoccoal disease if another vaccination campaign is not initiated.

The estimated basic reproduction ratio of 1.26 is low when compared to other diseases that New Zealand has experienced epidemics of (for measles it was estimated to be 12.8 (Roberts & Tobias, 2000), and 15.8 for pertussis (Roberts, 2000b)). As it is so low, we would expect that a vaccination campaign would be an ideal way to combat an epidemic. Even with the effective reproduction ratio being decreased below one through the effects of vaccination, it is not enough to eliminate the disease from the population, which results in future epidemics. As we have seen with the nation-wide vaccination campaign that ended in 2006, the incidence of infection decreased and this campaign could be implemented in the future to avoid another epidemic.

Chapter 8

Conclusions and Future Work

This thesis has explored a variety of mathematical models for vaccine preventable infections. The use of mathematical models to predict the number of people who could be infected (or prevented from being infected) under different vaccination campaigns is potentially a cost and life saving tool. Developing models that can be implemented and understood easily makes the use and results of these models accessible to a wide range of people.

The second chapter served as a general introduction to epidemic modelling, looking at the optimal vaccination schedule, rather than a particular infection. After introducing a vaccine into a population to combat a current or potential epidemic, a debate arises about whether to enforce vaccination or leave the decision to individuals. The choice of vaccination policy can cause two different outcomes for the community as whole; the best strategy for enforced vaccination may require a different proportion of the population vaccinated than if left to individuals to decide. Using game theory analysis we examined the proportion of the population that needs to be vaccinated in order to minimise the expected costs to the individuals and the community. Two different scenarios are considered, where vaccination lasts only one epidemic cycle and where vaccination is effective over an entire lifetime. An integral equation method was implemented to explore the proportion of the population that needs to be vaccinated in order to eliminate an annual epidemic disease, such as influenza, where the (non-vaccinated) population are susceptible each year and there was no lasting immunity from year to year. A differential equation model was implemented to explore the proportion needed to be vaccinated in order to eliminate an infection that is endemic in the population, such as tuberculosis, where one vaccination may last for life. For both cases we showed that if the expected cost of vaccination is less than the expected costs of being infected, the "break even" point for the two individual strategies (vaccinate or remain susceptible) occurs before the minimum cost to the community is reached – in terms of the proportion of the population vaccinated.

We then continued with our use of an integral equation model to look at the repeated

epidemics of measles in New Zealand. The population was split into four age classes, and the two time scales of the epidemic and demographics were split. The final size equation was solved if an epidemic occurred and then demographic changes were included to give us a year to year model. The final size equation was difficult to solve numerically, and we were forced to solve for the population as a whole then distribute the number of people infected according to the age class size. Ma & Earn (2006) showed that a solution exists to the final size equation in multiple dimensions, and Andreasen (2003) implemented an integral equation model with the two time scales to model influenza with cross-immunity. Andreasen & Frommelt (2005) used the integral equation method to investigate childhood epidemics, such as measles, but found that it gave different results to the SIR type model. More work can be included in this model in the future, to explore different methods for solving the final size equation in multiple dimensions, where it could be possible that an epidemic does not occur in all of the age groups. A multidimensional Newtons method could be implemented instead of the asymptotic expansion that we used.

It was our intention to continue using the integral equation method to model diseases with the carriage state, but as the use of this method for modelling measles was unsuccessful due to numerical limitations, we decided to use a differential equation approach for the rest of our modelling.

In the final chapters we used differential equation models to look at infections with a carrier stage – where people are infectious but show no outward signs of infection. The fourth chapter gave a literature review of models of the Hepatitis B virus, with a critical review of Medley *et al.* (2001). Our critique of Medley *et al.* (2001) found the conditions that are needed for the function that is used to calculate the proportion of the population who become carriers after being infected in order for a backwards bifurcation to occur. We then demonstrated that this model does not fit known data if we discretise the population into age groups. Including non-homogeneous mixing in the population allowed us to gain a better fit to the known data, as shown in our fourth chapter. However, the known data are a mixture of both acute infections and chronic carriers before the vaccination campaign was initiated, making it difficult to fit our model to. The models we presented, although not an exceptional fit to the know data, demonstrate some of the important aspects of Hepatitis B virus, and can be further extended to include other aspects such as high endemic areas compare to low endemic areas. Due to the nature of Hepatitis B virus transmission, structuring the population into age classes may not be the most effective modelling approach. Dividing the population into groups in terms of their risk of infection or transmission could yield results that more readily fit the known data, and would be more beneficial in terms of assessing the effects of a targeted vaccination campaign.

The last two chapters concentrated on modelling the epidemiology of meningococcal disease in New Zealand, and showing the effectiveness of the recent vaccination campaign. A number of compartmental models were presented, with the five age class SICR model with non-homogeneous model showing a good fit, but the inclusion of only temporary

immunity led us to our final model. Our model gave a basic reproduction ratio of only 1.2, suggesting that a vaccination campaign is a viable solution to eliminate any further epidemics from the population. As meningococcal B is a relatively new infection to the New Zealand population, the epidemic pattern is still in an oscillating phase before the infection becomes endemic. Our model showed that the two year vaccination campaign successfully reduced the number of people who would have been infected, but does not prevent another epidemic occurring in the future. However, we showed that by implementing a similar vaccination campaign to that that has already been carried out, as soon as the number of infections of meningococcal B begin to rise, the epidemic can be halted quickly. One of the major benefits of our model is that we are able to calculate the number of people who are carriers of the infection, who are the "silent" spreaders of the infection. Alterations to the model that could be included are a separate class for vaccinated individuals where they can still be carriers of the infection, and to allow different immune times for those who have been acutely infected, carriers or vaccinated. A spatially structured model may also be of benefit, as New Zealand has experienced areas of high meningococcal B prevalence and low prevalence. Again, this would allow us to see the effect of a more targeted vaccination campaign, as opposed to a nation-wide campaign.

Through both integral and differential equation models, we have investigated the epidemiology of different vaccine preventable diseases, concentrating on known situations in New Zealand. We have looked at what proportion of the population needs to be vaccinated in order to minimise the cost to individuals and to the community as a whole, through to the effect of the recent vaccination campaign on meningococcal B disease. Our hepatitis B and meningococcal B infection models could be expanded to capture some of the finer details of the infections we have studied, but they both gave a reasonable fit, as they are, to the known data. The integral equation method for a repeated epidemic infection could be expanded, and a different method used to solve the final size equation in multiple dimensions, but this is left for future work.

The main emphasis of this thesis was to explore the mathematical modelling of the effect of vaccination both on the course of an epidemic and on the proportion of the population that needs to be vaccinated to stop an epidemic. By using mathematical models to model the epidemiology of diseases, we can gain further insight to some aspects of the infection process that could otherwise be immeasurable - such as the number/incidence of carriers in the population and the effect that the carriers have on the epidemic. The results from this thesis could be used to predict the future of Hepatitis B and meningococcal B epidemics within New Zealand, and the methods outlined could be applied to other infections in any country.

Appendix: Elaborations to the community versus individual cost chapter

A.1 Derivation of the Final Size Equation from an SIR model

For the yearly vaccination scenario, we chose to use an integral equation model to gain the final size equation for the epidemic. However, we could have used a simple SIR model to gain the same equation. The derivation of this is shown below.

Let s be the proportion of people who are susceptible to infection, i be the proportion who are infected and r be the proportion who are removed. As we are dealing with an epidemic that is over within a year, we do not need to include any birth or death rates. So our system of equations is:

$$\begin{aligned} \frac{ds}{dt} &= -\beta is \\ \frac{di}{dt} &= \beta is - \gamma i \\ \frac{dr}{dt} &= \gamma i \end{aligned} \tag{A.1}$$

We have one redundant equation in the above system as there is no change in the population size. We want to find the proportion of people who are infected during the course of an epidemic. So we look at the change of infectious people with respect to susceptibles:

$$\frac{di}{ds} = -1 + \frac{\gamma}{\beta s} \tag{A.2}$$

Integrating this we gain:

$$i(t) - i(0) = -s(t) + s(0) + \frac{\gamma}{\beta} \log \frac{s(t)}{s(0)} \tag{A.3}$$

We let $t \to \infty$. We know that at the beginning of an epidemic $i(0)$ is approximately zero,

and then at the end of the epidemic there will be no more infected people left, so $i(\infty) = 0$.

$$0 = -s(\infty) + s(0) + \frac{\gamma}{\beta} \log \frac{s(\infty)}{s(0)} \tag{A.4}$$

The basic reproduction ratio for this system is given by $R_0 = \frac{\beta}{\gamma}$ (as infective people infect others at rate β and remain infective for an average time of $\frac{1}{\gamma}$).

$$\begin{aligned} R_0 \left(s(\infty) - s(0)\right) &= \log \frac{s(\infty)}{s(0)} \\ s(0) R_0 \left(\frac{s(\infty)}{s(0)} - 1\right) &= \log \frac{s(\infty)}{s(0)} \end{aligned} \tag{A.5}$$

At the start of the epidemic, the proportion of susceptible people is simply the proportion who have not been vaccinated, $1 - v$, and we define $R_v = (1 - v)R_0$ as before (Equation (2.9)). Substituting these into the above equation gives us the final size equation:

$$\log \left(\frac{s(\infty)}{1 - v}\right) = \left(\frac{s(\infty)}{1 - v} - 1\right) R_v \tag{A.6}$$

A.2 Yearly Epidemics, when C_V Greater than or Equal to C_I

For the yearly vaccinations, to find the proportion of people that need to be vaccinated to minimise the cost to the whole community, we need to minimise the cost function (Equation (2.17)), so we consider the derivative:

$$\frac{dC(v)}{dv} = \begin{cases} C_V - \left(1 + \dfrac{s(\infty)(R_0(1-v) - 1)}{(1-v)(1 - R_0 s(\infty))}\right) C_I & \text{if } 0 \leq v < 1 - \frac{1}{R_0} \\ C_V & \text{if } 1 - \frac{1}{R_0} < v \leq 1 \end{cases} \tag{A.7}$$

If the cost associated with being vaccinated is non-zero ($C_V > 0$), there will not be a critical point in the range $v \in \left(1 - \frac{1}{R_0}, 1\right)$, as can be seen from Equation (A.7).

In the range $v \in \left[0, 1 - \frac{1}{R_0}\right)$, a critical point occurs when:

$$\begin{aligned} \frac{C_V}{C_I} - 1 &= \frac{s(\infty)(R_0(1-v) - 1)}{(1-v)(1 - R_0 s(\infty))} \\ v &= \frac{C_V(1 - R_0 s(\infty)) - C_I(1 - s(\infty))}{C_V(1 - R_0 s(\infty)) - C_I} \end{aligned} \tag{A.8}$$

For Equation A.8 to hold, we need $\frac{C_V}{C_I} > 1$, as the right hand side is always positive in the region when $v \in \left[0, 1 - \frac{1}{R_0}\right)$. To classify this critical point, we shall analyse the second derivative of Equation (2.17):

$$\frac{d^2C}{dv^2} = \frac{R_0 s(\infty)(1 - v - s(\infty))(2 - R_0(1 - v + s(\infty)))}{(1 - R_0 s(\infty))^3 (1 - v)^2} C_I \tag{A.9}$$

At the critical point, the second derivative is given by (substituting Equation (A.8) into Equation A.9):

$$\left.\frac{d^2C}{dv^2}\right|_{v^*} = \frac{R_0C_V(C_VR_0s(\infty) - 2(C_V - C_I))}{C_I(1 - R_0s(\infty))} \tag{A.10}$$

The denominator of Equation (A.10) is positive, as $s(\infty) < \frac{1}{R_0}$ and $C_I > 0$, so we need to determine the sign of the numerator. Consider the case where it is positive:

$$\begin{aligned} R_0C_V(C_VR_0s(\infty) - 2(C_V - C_I)) &> 0 \\ \Rightarrow C_VR_0s(\infty) - 2(C_V - C_I) &> 0 \\ R_0s(\infty) &> \frac{2(C_V - C_I)}{C_V} \\ R_0s(\infty) &> 2 - \frac{2C_I}{C_V} \end{aligned} \tag{A.11}$$

As we are considering the case where $C_V > C_I$, we known $\frac{C_I}{C_V} < 0$. Thus:

$$\begin{aligned} -\frac{2C_I}{C_V} &> 0 \\ 2 - \frac{2C_I}{C_V} &> 2 \\ \Rightarrow R_0s(\infty) &> 2 \end{aligned} \tag{A.12}$$

This is a contradiction, as $R_0s(\infty) < 1$, so the numerator of Equation (A.10) must be negative, making the second derivative at the critical point negative, and giving us a local maximum when $C_V > C_I$ and $v \in \left[0, 1 - \frac{1}{R_0}\right)$. We have shown that the community cost will reach a maximum for some $v < 1 - \frac{1}{R_0}$ if $C_V > C_I$, as illustrated in Figure A.1.

When the cost associated with being vaccinated is equal to the cost associated with being infected, the two individual strategies will intersect when $s(\infty) = 0$, from Equation (2.18). The two strategies will tend towards each other as $s(\infty) \to 0$, which requires $R_0 \to \infty$. The minimum expected cost to the community would still occur when $v = 1 - \frac{1}{R_0}$ as can be seen from Equation (A.7).

A.3 Life-Long Vaccination, with C_V Greater than or Equal to C_I.

For life-long vaccination, we have the following expected costs:

$$\begin{aligned} E_V^L &= C_V \\ E_S^L &= \left(1 - \frac{1}{R_0(1-v)}\right) C_I \\ C^L &= \begin{cases} vC_V - \left(1 - \frac{1}{R_0} - v\right) C_I & \text{if } 0 \le v < 1 - \frac{1}{R_0} \\ vC_V & \text{if } 1 - \frac{1}{R_0} < v \le 1 \end{cases} \end{aligned} \tag{A.13}$$

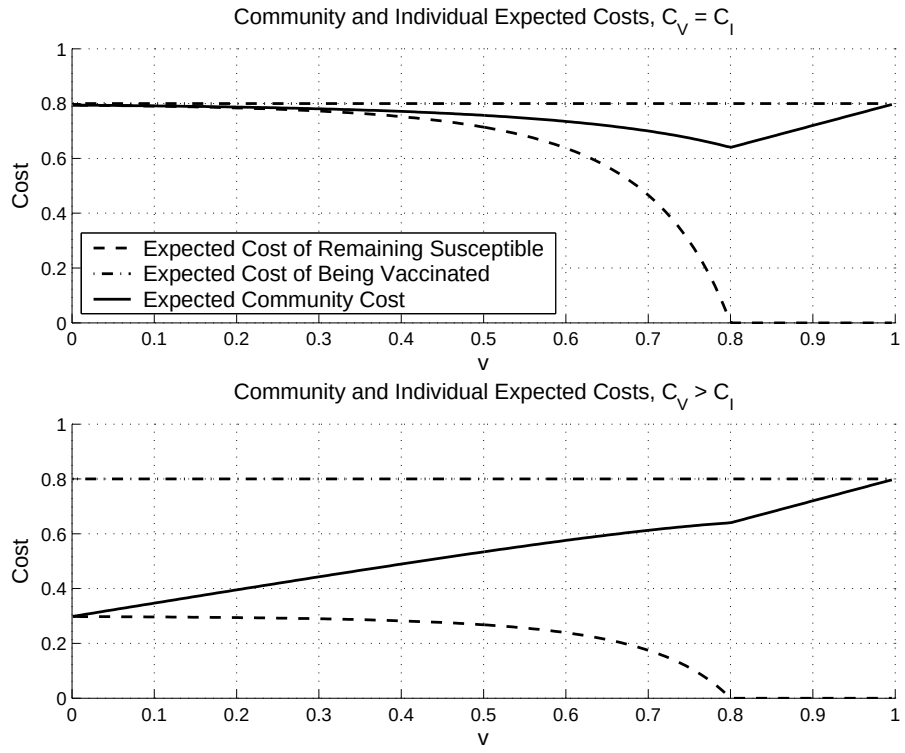


Figure A.1: Yearly Vaccination: If the cost of being vaccinated is greater than or equal to the cost of remaining susceptible, the individuals best strategy is always to remain susceptible - no matter what proportion of the population is vaccinated. The best strategy for the community is to vaccinate a proportion of the population equal to $1 - \frac{1}{R_0}$ if $C_V = C_I$, and not to vaccinate anyone if $C_V > C_I$. The legend is the same for both graphs.

If $C_V > C_I$, there will never be a "break even" point for the two individual strategies as the two strategies never intercept (illustrated in Figure A.2). The best strategy for the individual is to always remain susceptible, as this gives the minimum cost for all values of v.

For the community, the critical point will occur when the derivative of the cost function is zero. That is:

$$\frac{dC(v)}{dv} = \begin{cases} C_V - C_I & \text{if } 0 < v < 1 - \frac{1}{R_0} \\ C_V & \text{if } 1 - \frac{1}{R_0} < v < 1 \end{cases} \tag{A.14}$$

If $C_V \neq 0$, then the only time the derivative will be zero is when $C_V = C_I$, in which case the best strategy for the community is to vaccinate any proportion of the population in the range $\left[0, 1 - \frac{1}{R_0}\right)$. If $C_V \neq C_I$, and $C_V > C_I$, the best strategy for the community is to vaccinate no one.

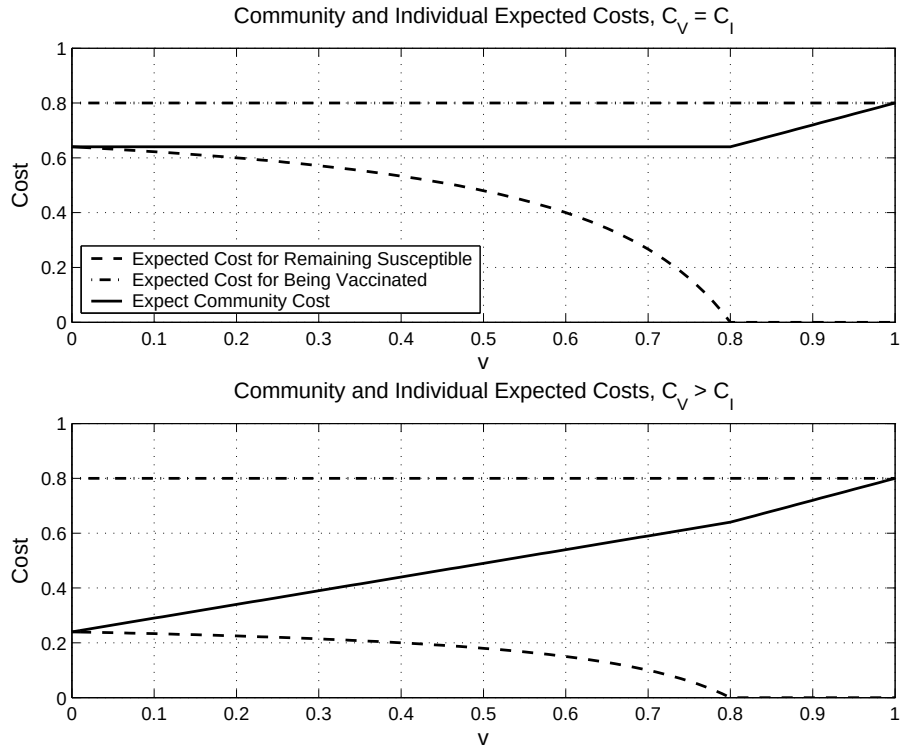


Figure A.2: Life-Long Vaccination: $R_0 = 5$, so there is only an epidemic if $v < 1 - \frac{1}{R_0}$. For both of the situations, $C_V = C_I$ and $C_V > C_I$, the best strategy for the community is not to vaccinate anyone.

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