Mathematical Models of The Spread of Hepatitis C Among Injecting Drug Users

The Effects of Heterogeneity

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BSc, MPhil

A thesis presented in fulfilment of the requirements of the degree of Doctor of Philosophy

March 2015

I dedicate this work to ...

my children AbduRahman, Fajer and Sulaiman

without whom this thesis would have been completed two years earlier,

my husband, Dr. Waleed Altuwaigri, and

my parents, Fwzan and Nora.

Acknowledgements

First and foremost I will thank Almighty GOD, the compassionate, the almighty Merciful, who kindly helped me to complete my thesis. It would not have been possible to write it without the help and support of the kind people around me, to only some of whom it is possible to give particular mention here.

Above all, I would like to thank my husband Waleed, my father Fwzan and my mother Nora for their unconditional love, great patience and personal support at all times. They have give me their unequivocal support throughout, as always, for which my mere expression of thanks likewise does not suffice.

The success of this thesis is attributed to the extensive support and assistance from my principal supervisor, Dr. David Greenhalgh. I would like to express my grateful gratitude and sincere appreciation to him for his guidance, valuable advice, supervision, encouragement and kindness to me throughout this study. Words are not enough to express my gratitude for the wonderful job he did. I am also grateful to my second supervisor Prof. Sharon Hutchinson for her good advice, support and guidance.

I take this opportunity to thank the Ministry of Education in Saudi Arabia through Princess Nora University (PNU) for making my PhD research program possible at the University of Strathclyde for their financial support during my studies. I would like to acknowledge the academic and technical support at the university of Strathclyde and its staff, particularly Dr Stephen Corson, Mr Ian Thurlbeck, Mrs Irene Spencer, Taghreed Jawa and all staff in the Mathematics and Statistics Department.

Finally, I extend my deepest thanks to my children AbduRahman (13 years), Fajer (7 years) and Sulaiman (3 years) for their patience, love, motivation and support when much needed, bedtime routine without Mama, and many "if you can please just give me one more hour to work on this ..." moments.

Abstract

The world faces an immense burden of hepatitis C virus (HCV) infection related morbidity and mortality. Transmission of HCV is ongoing, and the incidence of HCV infection has been increasing in recent years. Approximately 130 - 150 million people are estimated to be chronically infected with HCV and each year an estimated three to four million individuals are newly infected (WHO, 2013; Mohd Hanafiah et al., 2013). In developed countries, injecting drug users are considered as being at the highest risk of prevalence of HCV. Thus, this thesis describes the spread of HCV amongst injecting drug users. We use a mathematical model to study the effect of heterogeneity on the progress of the disease by dividing the population of addicts into p groups where they are sharing injecting needles in q shooting galleries and investigate the epidemic behavior of the virus. Moreover, we estimate the basic reproductive number R_0 and show analytically that HCV is controlled by this number R_0, if $R_0 \leq 1$ then the disease dies out and if $R_0 > 1$ the disease takes off in both addicts and needles and there is a unique endemic equilibrium. We look at analytical results on the effect of heterogeneity on the spread of HCV and optimal control of the epidemic by needle exchange and needle cleaning. Simulations with realistic parameter values estimated from data and the literature confirm the theoretical results and we numerically investigate the effect of heterogeneity on the spread of HCV. Then we extend the basic model to more realistic assumptions where addicts move in and out of groups, and investigate the HCV dynamic behaviour. We obtain similar analytical results again validated by simulations with realistic parameter values estimated from data and the literature.

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Chapter 1

Introduction and Literature Review

> "*I simply wish that, in a matter which so closely concerns the wellbeing of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide.*"
>
> Daniel Bernoulli 1766
>
> Bernoulli & Blower (2004)

It is nearly a quarter century since the Hepatitis C virus (HCV) was discovered. Hepatitis C is a blood borne liver disease, caused by the hepatitis C virus. HCV infection is a leading cause of chronic liver disease, including cirrhosis of the liver and liver cancer. Since its discovery in 1989, infection with HCV has been recognised as a major global health problem in many countries. According to the World Health Organisation (WHO), approximately 130 - 150 million people are estimated to be chronically infected with HCV and at risk of developing liver diseases including liver cancer (WHO, 2013), and each year an estimated three to four million individuals are newly infected and 350,000 deaths occur due to HCV related causes (Mohd Hanafiah et al., 2013).

HCV is transmitted primarily through direct percutaneous exposure to blood. In many countries, the two most common exposures associated with transmission of HCV are transfusion of blood from an unscreened donor and injecting drug use. The dominant source of new HCV infection in most developed countries is injection drug use (Shepard et al., 2005). Worldwide, recent estimates suggest that there may be between 11 and 21 million injecting drug users (Mathers et al., 2008), and HCV has been identified as the most common viral infection affecting injecting drug users (Crofts et al., 2001; Aceijas & Rhodes, 2007). Hence, as injecting drug use has created major international public health problems and individuals who inject drugs are the highest risk of infection of HCV, the work described in this thesis focusses on this risk group.

Recent years have seen an increasing trend in the number of publications that utilize mathematical models in epidemiology, with also increased understanding of what these models can provide and offer in terms of predictions. Mathematical models are being used to understand the disease dynamics, the transmission of infections and to evaluate the potential impact of control programmes in reducing HCV infections. Many studies have been modeled and established to understand the intricate relationship between the risk behaviour of injecting drug users and the transmission of HCV, global prevalence, treatment and therapy options. Thus this thesis shall discuss and explore the development and analyses of a mathematical model of the prevalence of HCV among drug users. Mainly we develop a deterministic, compartmental mathematical model to approximate the spread of HCV in an injecting drug

user population by Corson et al. (2012). In particular, we are interested in the effect of heterogeneity of the population of addicts who share injecting needles and syringes. In the following section, we outline briefly the work contained in this thesis.

1.1 Overview and Organization of the Thesis

In this thesis, we extend a mathematical model for the transmission of the HCV epidemic via needle sharing among people who inject drugs by Corson et al. (2012). Mainly, we shall discuss the heterogeneity effects where the people who inject drugs form a community of size n and they are divided into p groups according to their frequency of sharing injection equipment and they share m needles in q shooting galleries. Shooting gallery can be defined as a place where addicts meet to inject and share drugs. Our mathematical models are specified by a system of ordinary differential equations of different groups of various stages of infectivity of addicts and different stages of infectivity of needles. Then we move on to the main key parameter of our models, "The Basic Reproduction Number" which is denoted by R_0. This is the main parameter as it determines whether or not an infectious disease can spread through both populations of addicts and needles. After we have calculated R_0, scenario analyses are performed to predict the effect of changes in risk behaviours required to effect appreciable reductions in HCV infection and to minimise R_0. Special cases are also discussed in order to reduce the spread of the epidemic among addicts and needles being shared under special assumptions which give the minimum value of R_0.

This is followed by analytical results and a stability analysis of solutions of our

system of differential equations and initial conditions. We conclude this discussion with estimation of some parameters, and present numerical simulations of HCV prevalence and incidence among addicts and needles in Glasgow made by using the survey data in 1990 and 1993. In the next part of this thesis, we shall describe and extend our model by assuming that addicts are allowed to move in and out of the groups, and we look at the impact of transmission of HCV under this assumption. This is followed by presenting an expression for R_0 and some important dynamical results. Finally, we finish this chapter by showing some numerical results and simulations.

The thesis will be explored in seven linked parts. Firstly, attention is turned to set up the hypotheses of our model considering the impact of heterogeneity in Chapter Two, where the population of addicts is divided into p groups and each group has six different epidemiological categories. These groups are sharing m needles in q shooting galleries and leave the needles in three possible stages of infectivity. To examine the pattern of prevalence of HCV among addicts and needles, we set up a mathematical model of the transmission of an epidemic through needle sharing. The expression for R_0 is defined and special scenarios and cases are discussed which aim to minimise this parameter.

In Chapter Three, we shall analyse qualitatively the model system of equations to get insights into its dynamical features which will give better understanding of the effect of heterogeneity on the spread of HCV. The possible endemic equilibria of the system and the disease-free equilibrium are considered and discussed. We shall

also look at the local and global stability of these equilibria, as well as persistence of the disease.

Chapters Four and Five are aimed at the numerical simulations to assess the effects of heterogeneity between different groups of the population of drug users and different shooting galleries. We aim to do simulations using realistic parameter values estimated from the literature. We obtain the plots of infected addicts, needles and the antibody positive addicts in the cases where R_0 exceeds unity and is less than unity. In each figure we examined the prevalence of HCV and whether the disease dies out or persists. Chapter Six discusses the theoretical results that are obtained in Chapter Two numerically, computes the value of R_0 and presents numerical simulation in each scenario.

Driven by the fact that addicts are expected to move in and out of groups as they change their injection rate, we extend our model to consider this more realistic assumption. This extension is discussed and studied in Chapter Seven. A system of differential equations of HCV transmission among addicts and shooting galleries needles are generated, where the number of addicts in each group is a dynamic variable. Also, an expression for R_0, dynamical analysis and stability results, numerical work and simulation are discussed. The last chapter summarises our thesis, gives a general conclusion and also suggests some further work.

This completes our outline of the work contained in this thesis. In the rest of this chapter we will give a literature survey and present an introduction of HCV,

its discovery and transmission routes. This is followed by a brief discussion about HCV treatment and global prevalence of HCV. Then the impact of heterogeneity on infectious diseases dynamics will be discussed, as well as the use of mathematical models in epidemiology and R_0 as key parameter. This is followed by a summary of interventions to reduce the transmission of diseases (harm reduction policies). Finally, we shall present a review of some previous models of the prevalence of HCV among drug users.

1.2 Background of Hepatitis C Virus

HCV is a small, enveloped, single stranded, positive sense ribonucleic acid (RNA) virus. HCV can be classified as a member of the *flaviviridae* family of RNA viruses (Simmonds, 1999). There are six major HCV genotypes identified, every type of the six genotypes of HCV is unique with respect to its nucleotide sequence and response to therapy (Kamal & Nasser, 2008). Infection with HCV can cause both *acute* and *chronic* infections. The term of acute phase of HCV generally refers to the first six months of the infection. Since no obvious symptoms are noticed and there is no clinically apparent disease, many acute infections of HCV go undiagnosed. After this six month period, if acute infected individuals have detectable HCV, they are considered to have chronic phase HCV infection (Blackard et al., 2008). Nearly 80% of acute infection patients become chronically infected and about 20% will spontaneously resolve the infection (Chow & Chow, 2006).

1.2.1 Discovering Hepatitis C

For many years, patients suffered with end stage liver disease classified as *cryptogenic* cirrhosis, which meant that the reasons that had caused the liver disease are not known. Some people who received blood transfusions and developed hepatitis were diagnosed with non-A non-B hepatitis (NANB) (Gallin et al., 2000). In 1989, Michael Houghton and his team characterized and identified this non-A, non-B virus which was named as *hepatitis C* (Maddrey, 2000; Mahtab, 2012). This discovery represented a changing pattern in the field of infectious disease, which is the identification of an important human pathogen (Askari, 2007). Then blood banks started screening blood donors for hepatitis C in 1990. Nevertheless, it was not until 1992 that a blood test for hepatitis C was perfected that effectively eliminated HCV from the blood transfusion supply (Franciscus, 2010).

This discovery was an important and essential step to fighting this disease which causes a serious public health problem worldwide. Moreover, it led to successful efforts to develop a diagnostic test for HCV. Screening the blood supply was the highest priority. Indeed, this achievement allowed us to begin to understand the magnitude of the public spread of the disease. Unfortunately, although vaccines exist for hepatitis A and hepatitis B, there is no vaccine for the prevention of HCV infection, but several vaccines are currently under development (Strickland et al., 2008).

1.3 Routes of HCV Transmission

In order to reduce the risk of the spread of HCV, we shall understand how this virus infects people and what are the pathways that could transform a non-infected to an infected person. HCV is most likely to be transmitted through large volume or repeated direct percutaneous exposure to blood, for example through blood transfusion from infected donors, unsafe therapeutic injections or injecting drug use. Nevertheless, other routes such as sexual and perinatal transmission routes are also likely for possible cross contamination of blood from an HCV carrier to uninfected individuals (Tajima & Sonoda, 1996). The following groups are at known to be at increased risk for HCV infection (WHO, 2013):

1.3.1 Blood Transfusion Recipients

Historically blood product transfusion has been a major mode of transmission. Before 1992, when screening of blood donors for HCV was introduced, transfusion with blood or blood products increased the risk of transmission of HCV. The residual risk of post-transfusion of HCV has decreased from 1 in 5,000 to 1 in 103,000 since the introduction of blood screening donor programmes (Vogt et al., 1999). In England estimates for the frequency of HCV infected donations dropped from 1 in 520,000 (1993 - 1998) to 1 in 30 million (1999 - 2001) when all donations were tested for HCV RNA (Soldan et al., 2003).

1.3.2 Perinatal Transmission

Perinatal transmission of HCV has been the subject of many review studies. The perinatal transmission rate was 1.7% in infants of HCV antibody positive mothers irrespective of HCV RNA, 4.3% when the mother was HCV RNA positive (Yeung et al., 2001). In the study by Ohto et al. (1994) of the 53 antibody positive mothers (31 were positive for serum HCV RNA), three babies (5.6% of babies born to these mothers) become positive for HCV RNA. Although, there is evidence to suggest perinatal transmission of HCV exists, it was discovered recently that mother-to-child transmission has a lower risk, with consequences for the child which are poorly understood. Moreover, no prophylaxis against HCV transmission via mother-to-child is yet available.

1.3.3 Sexual Transmission

One of the most controversial areas of HCV is how much HCV can be transmitted by sexual activity. There are no published data sufficient to show whether sexually transmitted coinfections or particular sexual practices increase the likelihood of HCV transmission through sex (Tohme & Holmberg, 2010). Risk of HCV transmission by sexual contact differs by the type of sexual relationship. Persons in long-term monogamous partnerships are at lower risk of HCV acquisition (0% to 0.6% per year) than persons with multiple partners or those at risk for sexually transmitted diseases (0.4% to 1.8% per year) (Terrault, 2002). Although transmission of HCV through sexual intercourse with an infected person has not been proven, some studies and data suggest that it may occur. However, the risk of sexual transmission is limited which makes this group at low risk of HCV infection.

1.3.4 Percutaneous Exposure in Other Settings

There are a wide variety of other activities that may pose a risk for HCV transmission. These include tattooing, body piercing, acupuncture and intranasal drug use. Many researchers, who are interesting in tattooing and the risk of transmission of HCV, found that tattooing is associated with a higher risk of infection. Tattooing is associated with HCV infection, even among those without traditional HCV risk factors such as addicts and blood transfusion prior to 1992, and is more common among youths and young adults (Jafari et al., 2010). Health care workers are also judged to be among those at risk of HCV infection, though the reported prevalence is no greater than found in blood donors (Zuckerman et al., 1994). This suggests that there has not been significant occupational transmission of HCV to these health care workers.

1.3.5 Injecting Drug Use

The biggest risk factor cited for HCV transmission is injecting drug use. In developed countries, injecting drug use appears to play the main role in the spread of HCV, through blood to blood contact and sharing of injecting equipment. In a study of 716 injecting drug users, the prevalence among those who had injected for one year or less in 1998 - 1999 was 64.7% (Garfein et al., 1996). It has been found that HCV is more transmissible by needle stick puncture and sharing drug equipment than human immunodeficiency virus (HIV) (Hagan & des Jarlais, 2000). Prevalence estimates of HCV infection among drug users have been reported to be more than 50%. Furthermore, it appears that HCV has been identified as the most common viral infection affecting injecting drug users worldwide (Aceijas & Rhodes, 2007).

Consequently, the work in this thesis attempts to model the prevalence of this disease in the highest risk group which is injecting drug users. We aim to discuss and analyse the spread of HCV using mathematical models to understand, predict and control this infectious disease.

1.4 Treatment of HCV

Generally HCV infects a person silently, and this is one of the most difficult characteristics of HCV, that most infected individuals do not know that they have been infected as there are no clear symptoms and they do not feel ill and are unaware that they have been exposed to HCV. Over 80% of infected people with HCV develop a chronic infection (Chow & Chow, 2006). The infection of HCV can sometimes be cured. Treatment is aimed at eliminating the virus and slowing or stopping any progression or developing of the disease. The immediate goal of HCV treatment is to achieve a *sustained virological response* (SVR), defined by the continued absence of HCV RNA six months after completion of treatment (Fabry & Narasimhan, 2006; Puoti et al., 2013). The infection is cured in more than 99% of patients who achieve a sustained virological response (EASL, 2014).

At least six major HCV genotypes are identified. While genotype does not predict the result of HCV infection, it does predict the likelihood of treatment reaction and also may determine the duration of treatment (Simmonds, 1999; Fried et al., 2002). The chronic HCV infection can be treated with medication: the standard treatment is based on a combination of *peginterferon alpha* and *ribavirin*. In general, treatment

is expected to last for one to three months depending on the HCV genotype and other factors, administered for 48 weeks for HCV genotype 1, and for 24 weeks for HCV genotype 2 or 3 (McHutchison et al., 2009). The small percentage of infected individuals with chronic HCV infection would recover without treatment, and have the capacity to generate immune response against the virus (Elliott et al., 2006).

The clearance of the HCV infection is more likely to occur within three months after symptoms appear. Overall, the patients must be tested with a sensitive HCV RNA technique at the end of the treatment. Response to treatment is observed by important quantitative tests of HCV RNA after 4 and 12 weeks of treatment. At week 4, an undetectable HCV RNA level is defined as a rapid virologic response (RVR). At week 12, the undetectable HCV RNA level is defined as an early virologic response (EVR) (Bope & Kellerman, 2011). The endpoint of HCV treatment is a sustained virologic response (SVR), which correlates strongly with a permanent clearance of the virus and effectively a cure. Monitoring viral kinetics is useful for predicting whether or not the sustained virologic response (SVR) is likely to develop (Ghany et al., 2009).

1.5 Global Prevalence of HCV

Nearly 25 years since the discovery of HCV, it is now well established that HCV is of global importance affecting all countries, leading to a major global health problem that requires extensive active interferences for its control and prevention. Clearly, HCV has a worldwide distribution, occurring among persons of all genders, ages and regions of the world. For the estimation of the global burden of HCV, we need to

know about the prevalence of HCV infection in each country. These data should be determined based on community based researches, nevertheless, such data are lacking in most countries (Lavanchy, 2009).

In 1999 the World Health Organisation (WHO) estimated that the worldwide seroprevalence (positive HCV antibody) of hepatitis C infection was approximately 3%, with the virus infecting 170 million people, where nearly 150 million people are estimated to be chronically infected with HCV in 2013 (WHO, 1999, 2013). Based on submitted data and published studies, WHO has reported data on the world-wide prevalence of HCV infection. Globally, the highest prevalence rate of HCV was reported in Africa, with lower prevalence of HCV in Northern Europe . The lowest prevalence (0.01% - 0.1%) has been reported from countries in the United Kingdom and Scandinavia; the highest prevalence (15% - 20%) has been reported from Egypt (Alter, 2007). The most affected regions are Africa and East Asia and a lower prevalence has been estimated in North America, North and Western Europe and Australia. Developed countries with lower prevalence rate of HCV infection include the United Kingdom and Scandinavia (0.01%-0.1%), Germany (0.6%), Canada (0.8%), Australia (1.1%) and France (1.1%). On the other hand, a low but slightly higher prevalence rate of HCV infection has been reported in the United States (1.8%) and Japan (1.5% - 2.3%) (Wasley & Alter, 2000; Shepard et al., 2005; Alter, 2007).

1.5.1 Global Prevalence of HCV amongst Injecting Drug Users

In 2007, Aceijas and Rhodes reviewed data on HCV prevalence among injecting drug users in 57 countries and in 152 sub-national areas. They found reports of HCV prevalence of at least 50% among addicts in 49 countries (Aceijas & Rhodes, 2007). Later in 2011, Paul Nelson and colleagues review 4,386 reviewed sources and 1,019 literature sources to estimate national, regional, and global prevalence and population estimates for hepatitis B (HBV) and hepatitis C (HCV) among injecting drug users (Nelson et al., 2011). The investigators provide a review about HCV prevalence data from 77 countries of the 152 countries where there were injecting drug users populations, these countries hold 82% of the estimated population of injecting drug users of the world. This study states that 10 million injecting drug users might be positive for HCV antibodies and more than 80% of injecting drug users in 12 countries are estimated to be HCV infected, and HCV antibody prevalence was 60 – 80% in injecting drug users in 25 countries (Nelson et al., 2011). Table 1.1 summarises the results of worldwide HCV prevalence amongst injecting drug users by region ranged according to the study of Aceijas and Rhodes (2007), whom undertook a review of grey and published literature from 1998 to 2005 on the global prevalence of HCV antibody and HIV/HCV co-infection among injecting drug users.

Region	HCV prevalence amongst drug users
Middle-East and North Africa	5 - 60%
Eastern Europe and Central Asia	10 - 96%
South and South-East Asia	10 - 100%
East-Asia and Pacific	34 - 93%
Latin America	2 - 100%
North America	8 - 90%
Australia and New Zealand	25 - 88%
Western Europe	2 - 93%

Table 1.1: HCV prevalence estimates among injecting drug users by region (Aceijas & Rhodes, 2007).

Now, we shall discuss some results in these reviews of the spread of HCV among injecting drug users.

1.5.1.1 Middle-East and North Africa

The prevalence of HCV among addicts has been estimated with the highest rate in Israel 67%, and the lowest is in Turkey 28.9%. Both Saudi Arabia and Egypt are estimated as 49.8% and 49.4% respectively (Nelson et al., 2011). Another study states that HCV prevalence among injecting drug users in Egypt is 63% (El-Ghazzawi et al., 1994). In the Aceijas and Rhodes (2007) global review, the high estimates of HCV prevalence came from Syria, 60%, where there are approximately 800,000 addicts, and the lowest prevalence is in Lebanon, 5%, where there are 440,000 addicts. This study has reviewed only three countries in this region (Syria, Lebanon and Israel).

1.5.1.2 Eastern Europe and Central Asia

The estimation of HCV prevalence in Eastern Europe, Aceijas and Rhodes (2007) report that Bulgaria and Estonia have the highest rate with 60-95% and 95.5% prevalence respectively. The lowest estimation rate is obtained from Hungary at 6-31%, with 25,000 addicts. The same result is reported in the review of Nelson et al. (2011). Also, this review shows that Estonia and Russia have the highest rates of HCV prevalence at over 90%, as Russia has the highest number of injecting drug users in this region between 1.5 and 3 million addicts (Nelson et al., 2011). In Central Asia, Aceijas and Rhodes (2007) report that Kazakhstan has the lowest rate, 38%, and Turkmenistan has the highest, 46.2 - 74.4%.

1.5.1.3 South and South-East Asia

Thailand records the highest rate of HCV prevalence among injecting drug users with 89.8% prevalence. Both Singapore and South Korea have the lowest rate as both prevalences of HCV are less than 50% (Nelson et al., 2011). According to Aceijas and Rhodes (2007), Thailand has high rate of prevalence of HCV at 89%, also India and Indonesia have more than 90% prevalence of HCV among injecting drug users, with also high number of addicts (Indonesia 562,000 addicts and India 1,163,000 addicts).

1.5.1.4 East-Asia and Pacific

HCV prevalence estimates in China at 33.53-99.3% are the highest rate reported by Aceijas and Rhodes in the East-Asia region, also China records the highest number of injecting drug users at 1,928,000. Japan, Hong Kong and Taiwan have a high rate of HCV prevalence of more than 50%. The result of the estimations of HCV in

Japan and China in Nelson et al. (2011) are similar, at 64.8% and 67% respectively. The lowest rate is in Taiwan with 41% (Nelson et al., 2011).

1.5.1.5 Latin America

The lowest estimate for the prevalence of HCV in this region is for Paraguay 9.8%, the highest rate is for Mexico with 97.4% then for Brazil 63.9% (Nelson et al., 2011). In another review by Kershenobich et al. (2011) the estimation of HCV prevalence in Sao Paulo is 11% among injecting drug users.

1.5.1.6 North America

The global review of Nelson et al. (2011) indicates that the prevalence of HCV in injecting drug users is over 60%, where in Canada it is 64% and in the United States it is 73% (Nelson et al., 2011). Aceijas and Rhodes report that these rates are from 8% to 88% in the United States and 46% to 90% in Canada.

1.5.1.7 Australia and New Zealand

In a study by Law et al. (2003), the estimation of HCV prevalence among injecting drug users is 83% in Australia. Both Australia and New Zealand have a similar HCV estimation rate in the global review by Nelson et al. (2011), at 54.6% and 51.9% respectively. According to the review of Aceijas and Rhodes (2007), these rates are between 80% to 84% in New Zealand, and from 41% to 60% in Australia.

1.5.1.8 Western Europe

The prevalence rates of HCV prevalence in Western European injecting drug users reported in the review by Matheï et al. (2002) ranged between 37% and 98%. The

HCV prevalence in injecting drug users where there are the highest number of addicts estimated is in Spain, where there are 290,000, the HCV prevalence is in the range 59.5% to 85%. Then comes Germany with rate 82.5% where there are nearly 200,000 addicts. The lower rate of HCV prevalences are estimated in the UK (21.3-59%) and Austria (26.3-33.1%) (Aceijas & Rhodes, 2007).

We have completed our discussions on the biology and epidemiology of HCV infection. In what follows we shall discuss mathematical models in epidemiology. The first section will discuss the structure of the mathematical model, then we shall present some of the key concepts and techniques involved in the modelling of infectious diseases. Secondly, we will look at the fundamental concept of modelling, R_0, followed by a discussion of heterogeneity and its impact on the dynamic of diseases. Examples of mathematical models on the heterogeneity will discussed, two models by Diekmann et al. (1990) and Greenhalgh (1996) will be reviewed briefly.

1.6 Epidemiology Mathematical Models

Epidemics of infectious diseases have been documented throughout history. The first person to mathematically study the spread of infectious diseases was Daniel Bernoulli (1760); this work was intended to evaluate the effectiveness of smallpox variolation (Bailey, 1975). Recently, mathematical models have long been important tools for understanding and controlling the spread of infectious diseases. The mathematical models used to understand, forecast and control the spread of infectious diseases such as HCV are diverse and growing rapidly. Also, these models are used to understand the transmission of infections and to evaluate the potential impact of control

programmes in reducing morbidity and mortality. One of the fundamental purposes for studying infectious diseases is to improve control and ultimately to eradicate the infection from the population. Thus models can be a powerful tool in this approach and allow us to optimize the use of limited resources (Keeling & Rohani, 2011).

Mathematical models can take many forms, however they essentially describe a system through mathematical equations. They allow studying how a system changes from one state to the next, as well as the relation between variables used in the equations that define the system (Hens et al., 2012). In the application of models of infectious disease, Hens et al. distinguished two primary aims of these models: forecasting and understanding. They meant by forecasting that projections are made of the number of infections and their consequences under various scenarios of interest. By understanding Hens et al. meant that models are used that mimic a particular process for the development or transmission of infectious diseases with the aim to improve the knowledge of the process itself, rather than produce estimates of outcomes of this process. One of the types of models is a deterministic model. In this model the states of the system are the expected values of the outcomes. Thus deterministic models represent the expected or average behaviour of the system.

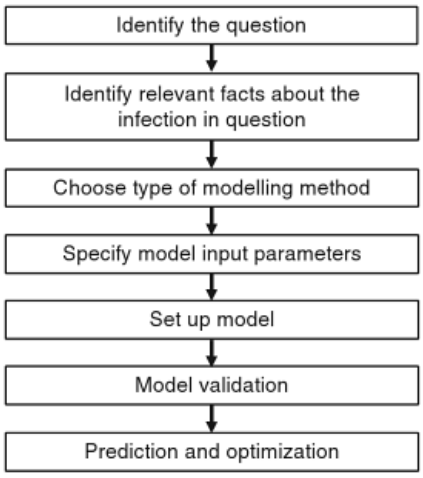


Figure 1.1: Steps in the setting up and development of a model (Habbema et al., 1996; Vynnycky & White, 2010).

1.6.1 Model Structure

In 1938, John Synge gave a description of applied mathematics to set the stage and structure of mathematical modelling. He noticed that there are three stages in any theory in applied mathematics including mathematical modelling: (i) creation of mathematical formulation of axioms or laws, (ii) mathematical deductions of the behaviour of the model, (iii) comparison of these deductions with observations (Synge, 1938). The success of the model is to include sufficient complexity to make the model valuable, but simple enough to understand, which necessarily requires that an understanding is developed of the importance of various processes in determining model behaviour. To illustrate how models are set up, Figure 1.1 shows a list of key steps which might be involved in setting up and developing a model. Each step may need to be reused many times until the model is completed and achieves its target.

1.7 The Basic Reproductive Number R_0

The basic reproductive number, R_0, is one of the fundamental concepts in mathematical biology. In 1911, Ronald Ross studied and established a model of malaria transmission, and gave the standard incidence ratio and the *basic reproductive number* (Ross, 1911; Fu et al., 2013). In epidemiology, the basic reproductive number of an infection is the number of cases that one case generates on average over the course of the infectious period. The roots of the concept can be traced through the work of Alfred Lotka, Ronald Ross and others, however its first modern application in epidemiology was by George McDonald in 1952, who modeled the spread of malaria (Macdonald, 1952; Fu et al., 2013).

The concept of R_0 is fundamental to the study of the simple models, those without complicating heterogeneity. This parameter measures the intrinsic ability of a parasite to invade and persist in specified host populations (Anderson & May, 1992). It comprises aspects of the three basic factors determining the epidemiology of an infectious disease (Dowdle & Hopkins, 1998):

- The natural history of infection.
- The route of transmission.
- The environment and behaviour of the population.

The basic reproductive number R_0 is defined as the expected number of secondary cases produced by an index case in a completely susceptible population at equilibrium (Dietz, 1993), which is a measure of the potential for diseases to spread within

a population. If R_0 is less than unity then a few infected individuals introduced into a completely susceptible population will, on average, not spread. On the other hand, if R_0 exceeds unity, then the number of infected individuals will increase with each generation and the disease will spread (Dietz, 1993; Diekmann et al., 2012).

This number is the initial growth rate, when we consider the population on a generation basis with infecting another host compared to begetting a child (Diekmann et al., 2012). R_0 is a threshold parameter for invasion of a disease organism into a virgin population of susceptibles. In many disease transmission models the highest prevalence of infected hosts and final size of the epidemic is an increasing function of R_0 making it a good measure of spread (Brauer et al., 2008). Because of the important role R_0 has played in understanding and predicting epidemic behaviour, the concept has been generalized to account for heterogeneity and a more complex description of the infection process. Techniques to calculate threshold values from theoretical models include the eigenvalues of the Jacobian matrix, the existence of the endemic equilibrium, and the constant term of the characteristic polynomial. R_0 can also be estimated from epidemiological data via the number of susceptibles at the endemic equilibrium, over the average age at infection (Li et al., 2011).

Overall, no other concept has so effectively transcended mathematics, biology, epidemiology, and immunology than R_0. No other concept is so general that it can be understood in terms of compartment models, network models, and partial differential equations. The threshold nature of R_0 is used to monitor and control severe real-time epidemics. Control measures are often deemed adequate if $R_0 \leq 1$, making

the problems with R_0 more than just theoretical. In conclusion, R_0 is a quantity that relates to the initial phase of an epidemic. This makes practical sense in terms of disease prevention.

1.8 Heterogeneity Models

It has long been understood that the heterogeneity of a population with respect to factors that may enhance or inhibit the transmission of infections may influence the effectiveness of strategies to control such infections (Anderson & May, 1992). Heterogeneity is the primary complexity complicating model structure, both between individuals in terms of risk of infection from other members of the population and in pathogens. This is an area of active research in infectious diseases epidemiology that is focused on a variety of potentially important problems (Dowdle & Hopkins, 1998). Therefore, it is important to allow individual heterogeneity in statistical and mathematical models of infectious disease. Such models often involve specifying contact rates between individuals (Farrington et al., 2013).

The heterogeneity of the population itself can play an important role in the spread of an epidemic. Often the heterogenous population is divided into subgroups, each of which is homogenous in the sense that group members have similar characteristics. The division of the population into groups might be based not only on disease related factors, such as latent period, infectious period, route of transmission and amount of vaccination, but also on social, economic, cultural or geographic factors (Dushoff & Levin, 1995; Hethcote, 1996). Most of the heterogeneity in disease transmission is based on difference in the social behaviour of the population at risk for the

disease. Hence, often the division of the population is based on the question:"Who mixes with whom?" (Hethcote, 1996). Many epidemiological models have been formulated with multiple groups and have defined contact matrices for the interaction between individuals of the groups, such models by Lajmanovich and Yorke (1976), Nold (1980), Dushoff and Levin (1995) and Greenhalgh (1996). We shall present an overview of some important works which include the effect of heterogeneity in modeling infectious disease.

1.8.1 Examples of Heterogeneity Models of Infectious Diseases

Models of infectious diseases can provide valuable insights into how infectious diseases spread and are controlled.

The work by Diekmann et al. (1990)

Because of the important role the basic reproductive number has played in understanding and predicting epidemic behaviour, Diekmann et al. (1990) develop the theory of how to define and compute the basic reproductive number R_0 in models for infectious diseases in heterogeneous populations. Thus, this study attempted to compute R_0 in more complicated models involving heterogeneity in the population. In general situations, the analysis of Diekmann et al. shows that R_0 is given by the maximum eigenvalue of the "next generation operator". This method converts a system of ordinary (or partial) differential equations of a model of infectious disease dynamics to an operator that translates from one generation of infectious individ-

uals to the next. The basic reproductive number is defined as the spectral radius (maximum eigenvalue) of this operator.

The Model of Greenhalgh (1996)

As a specialist work on the infectious diseases, Greenhalgh (1996) modeled the effects of heterogeneity on the spread of HIV/AIDS among a population of injecting drug users. This model allowed injecting drug users to visit shooting galleries with variability in the rate at which they visit shooting galleries, their choice of shooting gallery, and whether or not they clean their needles before use.

Later in another study, Greenhalgh & Hay (1997) considered an analysis of an extended version of the basic model by Kaplan (1989), to allow for the possibility of infectious drug users not always leaving a needle infected and the likelihood that HIV positive addicts stop or reduce their amount of sharing injecting equipments. Greenhalgh (1996) modified the assumptions of the basic model of Kaplan who assumed that all addicts behave exactly the same and all needles (equivalently all shooting galleries) are exactly the same (Kaplan, 1989). In this model the population of n addicts is divided into p groups of sizes $n_1, n_2, \ldots, n_p$ where $\sum_{i=1}^{p} n_i = n$, and the size of the different groups of drug users remained constant. Similarly, there are m needles in q shooting galleries of sizes $m_1, m_2, \ldots, m_q$ where $\sum_{j=1}^{q} m_j = m$. For $i = 1, 2, \ldots p$ and $j = 1, 2, \ldots q$ and where $\Lambda_{ij} = \lambda_i p_{ij} n_i / m_j$, the differential equations

which described the spread of the disease are:

$$\frac{d\pi_i}{dt} = (1-\pi_i)\left(\sum_{j=1}^{q}\lambda_i p_{ij}(1-\xi_{ij})\alpha\beta_j\right) - \mu\pi_i, \tag{1.1}$$

$$\frac{d\beta_j}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_i - \sum_{i=1}^{p}\Lambda_{ij}\beta_j\Big(1-(1-\pi_i)(1-\xi_{ij}(1-\theta)\Big), \tag{1.2}$$

with suitable conditions $1 \geq \pi_i(0) \geq 0$ and $1 \geq \beta_j(0) \geq 0$. The descriptions of the model parameters are presented in Table 1.2. Recall that R_0 is the key parameter which determines the behaviour of the disease. Greenhalgh (1996) found that R_0 is the largest eigenvalue of this $q \times q$ matrix Q_{jk}, where:

$$Q_{jk} = \sum_{i=1}^{p}\frac{\Lambda_{ij}(1-\xi_{ij})}{\sum_{s=1}^{p}\Lambda_{sj}\Big(1-(1-\theta)(1-\xi_{sj})\Big)}\frac{\alpha}{\mu}\lambda_i p_{ik}.$$

$\rho(\mathbf{Q})$ is the spectral radius of the matrix $\mathbf{Q}$ which is $q \times q$ with $Q_{jk} \geq 0$ for $j,k = 1,2 \ldots q$. $\rho(\mathbf{Q})$ is defined to be the largest eigenvalue of the matrix $\mathbf{Q}$.

The principal result in this model is if $R_0 \leq 1$ the system of equations (1.1) and (1.2) has a unique equilibrium solution where the disease has died out in each group of addicts and in each shooting gallery, and if $R_0 > 1$ and disease is initially present in either addicts or needles then the fractions of infected addicts and the fractions of infected needles tend to their unique equilibrium values. Then, Greenhalgh looked at the effect of altering the assumptions that the different groups of addicts were of constant sizes throughout the epidemic by introducing recruitment of susceptible addicts into the population and deaths of individuals infected with AIDS. He found that the equilibrium results were similar to the model with constant

size population groups. The threshold value is the same as for the model with constant size populations groups, with n_i, the size of group i, replaced by its disease-free equilibrium value.

Parameter	Denotation
θ	Probability that a susceptible addict flushes an infectious needle.
π_i	Fraction of type i addicts that are infected.
β_j	Fraction of needles in shooting gallery j.
ξ_{ij}	Probability that addict of type i effectively bleach cleans needle j before use in shooting gallery.
λ_i	Rate of addicts of type i visit shooting galleries.
α	Probability of HIV transmission via shared needles.
p_{ij}	Probability that addict i chooses shooting gallery j.
μ	Rate of joining and leaving sharing, injecting population per addict.

Table 1.2: Descriptions of parameters in model of Greenhalgh (1996).

1.9 Harm Reduction

The term *harm reduction* refers to policies, programmes and practices that aim to reduce the adverse health, social and economic consequences of the use of legal and illegal drugs. Harm reduction applied to substance use, such as injecting, is a form of secondary prevention. It aims to prevent the consequence of drug use, that is, to reduce the burden of disease and improve the health of the population (Lenton & Single, 1998). These approaches for injecting drug use focus on the harms associated with injecting: blood-borne viruses such as HIV and HCV. The current harm

reduction approach has its roots in the spread of HIV infection among drug users in the mid-1980s. This was a time when health workers started providing clean needles to injecting drug users, rather than seeking to achieve their abstinence from drug use in order to halt the spread of HIV (Abadinsky, 2010; Rehm et al., 2010). The United Kingdom, Australia, Switzerland, The Netherlands and Canada have been early adopters of the harm reduction strategies (Ritter & Cameron, 2006), and many countries in Asia, Latin America and Eastern Europe are encouraged to follow these policies. Nowadays, there is a need to provide people who inject drugs with options that help to minimise risks from continuing to use drug and of harming themselves or others.

In 2006, Ritter and Cameron presented a systematic review on the effectiveness of harm reduction for injecting drugs, alcohol and tobacco, where the majority of the literature concerned injecting drugs. In this review, Ritter & Cameron (2006) found that harm reduction has solid efficacy, effectiveness and economic data that support needle syringe programmes and outreach programmes in the area of injecting drugs. Outreach is defined as contacting drug users in the society where they live. The principles and keys of harm reduction on injecting drugs include: there is acceptance that drugs are a part of society, the main target is reducing harm rather than drug use. Harm reduction should provide a comprehensive public health framework. As we mention above, HCV is a comparatively common blood-borne infection that is primarily transmitted through injecting and sharing drugs. In the United Kingdom 80% of HCV infections are due to injecting drug use (de Angelis et al., 2009; Ritter & Cameron, 2006). The risk of becoming infected with HCV increases with inject-

ing duration. Thus, two key harm reduction interventions that may reduce HCV transmission are (Turner et al., 2011):

(i) Needle and syringe programmes (NSPs).

(ii) Opioid substitution treatment (OST).

NSPs aim to reduce the use and sharing of injecting equipment that may be infected with HCV, where OST aims to reduce injecting frequency and thereby reduce the probability of sharing and increase coverage of NSPs. A combination of NSPs, OST and treatment of injecting drug users of HCV has been argued to play a role in the reduction of the incidence and prevalence of the infection of HCV (Martin et al., 2011; Tod & Hirst, 2014).

1.9.1 Needle and Syringe Programmes (NSPs)

Needle and syringe programmes can be defined as providing sterile injecting equipment to inject drug users. This facilitates the use of clean needles and syringes and reduces the number of injections with used needles and syringes (WHO, 2012). NSPs are one of the main harm reduction measures that aim to curb the spread of blood-borne viruses such as HIV and HCV among injecting drug users. In the review of Ritter & Cameron (2006), NSPs have the record as the most widely cited and researched harm reduction intervention. For those who continue to inject, NSPs based in drug services and chemists provide clean injecting equipment (NICE, 2014). Ritter and Cameron described the literature as being predominantly positive with respect to HCV control, although NSPs are predicted to have little impact on HCV incidence and prevalence compared with HIV (Pollack, 2001). However, there is limited evidence to support the effectiveness of NSPs in preventing HCV transmission.

Lack of evidence in support of these programs does not necessarily mean that NSPs are ineffective (Turner et al., 2011). On the other hand harm reduction practices including NSPs are sufficient to keep HIV prevalence at a very low level. The HCV virus is so much more easily transmitted than HIV that HCV prevalence can be very high and HIV prevalence very low even in populations following similar practices (Weimer & Vining, 2009). Overall, NSPs might be the most strongly identified harm reduction programme and the body of evidence is very strong towards their efficacy and effectiveness (Pollack, 2001; Ritter & Cameron, 2006).

1.9.2 Opioid Substitution Treatment (OST)

Opioid substitution treatment is the primary pharmacological treatment option for opioid dependence. OST can be considered as one of the most effective interventions in controlling drug dependence that improve health and social functioning; it also can reduce illegal drug use and the frequency of injection (WHO, 2012). A number of different opioid agonists are used for OST, the most common is methadone, which was first widely used in the 1960s as a drug for those dependent on heroin (Csiernik, 2011). The basis for use of methadone is that individuals receiving methadone would have no need to use heroin or to be involved with various behaviours needed to maintain heroin addiction. Methadone does reduce heroin use, non-opioid drug use and health problems (Sees et al., 2000; WHO, 2012).

Recent pooling of UK studies by Turner et al. (2011) has suggested that exposure to high NSPs coverage and OST each alone approximately reduced the risk of HCV infection by 50%, and together in full harm reduction of NSPs plus OST

may reduce harm by 80% among injecting drug users. In conclusion, there is good evidence that uptake of OST and NSPs can substantially reduce the risk of hepatitis C virus transmission and prevalence of HCV among injecting drug users (Martin et al., 2011; Turner et al., 2011; Vickerman et al., 2012a).

The Work by Vickerman et al. (2012a)

In 2012, Vickerman et al. developed a model to estimate the impact of OST and NSPs on HCV prevalence among injecting drug users. The model simulated the movement of addicts between different intervention and HCV infection states. Addicts are tracked through four different states of: no intervention, OST only, NSPs only and a combination of OST plus NSPs. In general impact analysis, the model of Vickerman et al. (2012a) projected the effect on HCV prevalence of three coverage levels of OST and NSPs 20%, 40% or 60% for each, for three chronic HCV prevalence scenarios 20%, 40% and 60% with no OST or NSPs at baseline. The HCV prevalence scenarios were achieved by varying the baseline force of infection. For a baseline chronic HCV prevalence of 20%, 40% or 60% the model suggested that NSPs and OST can reduce HCV transmission by 30%, however required the coverage of each intervention to be more than 60% for 15 years or more than 40% for 20 years. Although other studies have suggested that HCV prevalence can be reduced through intervention (Turner et al., 2011), some studies emphasized the difficulty in reducing HCV transmission to low levels (Murray et al., 2003). Scaling up NSPs and OST can reduce HCV incidence among injecting drug users, however this reduction can be modest and requires long-term intervention coverage and many years to occur.

1.10 Prevalence of HCV in People with HIV

In the area of current epidemics and endemicity, coinfection with HIV and HCV is a significant problem. These two viruses are similar in a number of ways, and are highly prevalent amongst injecting drug users, as both viruses are transmitted easily by exposure to infected blood. In general, the level of infection of HCV amongst HIV-infected injecting drug users is much higher than HCV infection amongst injecting drug users not infected with HIV, although the transmission route of both diseases is spread by high risk injecting drug users (Vickerman et al., 2010). According to the Centers for Disease Control and Prevention (CDC), about 25% of individuals infected with HIV are also infected with HCV, and 50% - 80% of addicts are infected with HCV within the first five years of starting to inject drugs (CDC, 2002).

It has been estimated that approximately three million drug users might be living with HIV (Mathers et al., 2008). On the other hand, ten million drug users might be infected with HCV (Nelson et al., 2011). In the review of Hagan & des Jarlais (2000), among injecting drug users worldwide, HIV prevalence varies from 5 - 80%, with annual HIV incidence between 1 - 50%. More consistency is shown in HCV prevalence (50 - 90%) and annual HCV incidence (10 - 30%). Host, environmental and viral factors that favor rapid spread of HCV among addicts suggest that HCV infection in a population of injecting drug users may become endemic over a relatively short period of time. Lower transmission efficiency for HIV also indicates that its spread among injecting drug users may be somewhat slower (Hagan & des Jarlais, 2000).

Prevention of primary infection with HIV and HCV is critical to reduce long-term disease rates in injecting drug users. HIV and HCV amongst injecting drug users are strong justifications of the policy of harm reduction. Also the expansion of NSPs ensured people did not share injecting equipment and thus transmit blood-borne viruses such as HIV and HCV. Moreover, the provision of OST enabled people dependent on opiates such as heroin to move away from heroin use and injecting with the attendant health risks (MacArthur et al., 2014; NAT, 2013). As we discussed above, there are recent studies indicating that the combination of OST and NSPs can significantly reduce both HCV and HIV incidence (van den Berg et al., 2007; Turner et al., 2011; Vickerman et al., 2012a). However, there is an order of magnitude difference in transmissibility and prevalence between HIV and HCV in injecting drug users, therefore levels of intervention coverage that prevent HIV may not necessarily prevent HCV infection (Murray et al., 2003).

1.11 Examples of Mathematical Models

In this literature review we briefly outline some of the previous work on mathematical modeling of the spread of HCV amongst injecting drug users. First we shall look at some models of the spread of HCV and HIV, then we will outline some mathematical models of the spread of HCV.

1.11.1 Models that Examine the Spread of HCV and HIV amongst Injecting Drug Users

As worldwide systematic ecological analysis by various authors has shown that there is a strong positive relationship between the prevalence of HIV and that of HCV in different injecting drug users populations, we shall discuss some models that examine the spread of HCV and HIV amongst this high risk population.

The model by Vickerman et al. (2009)

Deterministic compartmental models are developed to simulate the transmission of HCV and HIV amongst injecting drug users in Rawalpindi, Pakistan with different levels of needle and syringe sharing (Vickerman et al., 2009). The model by Vickerman et al. was used to project the future HCV and HIV epidemics and estimate the potential impact of a generic intervention measure, which eases the level of needle and syringe sharing, on the prevalence of HCV and HIV amongst injecting drug users populations. Moreover, it was used to investigate why the prevalence of HCV amongst injecting drug users in Rawalpindi was low despite the widespread reporting of needle and syringe sharing.

The model projections suggest that the low HCV prevalence in Rawalpindi is probably due to most HIV/HCV transmissions occurring in a small addicts' subgroup that shares needles and syringes frequently with strangers, with most needle and syringe sharing incidents being low risk. In the HCV model the addicts' popu-

lation was stratified by: (1) HCV infection status, frequency of needle and syringe sharing: do not share, share at low levels, share at high levels, and (2) length of injecting career: recent initiates and long term injectors. Susceptible addicts, once infected with HCV, were assumed to progress to an acute stage of infection. A proportion of these newly infected addicts were assumed to progress to an acute stage where they can spontaneously resolve their infection while the remaining proportion of these newly infected addicts progress to an acute stage of infection which leads to chronic HCV infection. The model assumed that, of addicts who can spontaneously resolve their infection, a proportion become immune to HCV re-infection, and the remaining proportion were assumed to become susceptible to HCV re-infection.

Vickerman et al. continued to stratify the population by frequency of needle and syringe sharing and length of injecting career in the HIV model. This model assumed that once a susceptible addict is infected with HIV he or she progresses to a stage of infection where they have high levels of HIV. They are then assumed to progress to a longer lasting infectious class where they have much lower levels of HIV. At the end of this, the infected addict progresses to another stage of infection with high levels of HIV, after which they develop AIDS.

The model suggested that most of the needle and syringe sharing events in Rawalpindi are such that the risk of HCV transmission is relatively low. However, there is a small group of high risk addicts that share more frequently with strangers, hence the high prevalence of HCV-HIV co-infection. Projections suggest that the prevalence of HIV in injecting drug users will increase to 5 - 12% by 2015, and the

prevalence of HCV will increase if HIV increases HCV transmission. Also, any intervention measures employed to reduce the sharing of needles and syringes would need to achieve a sustained and substantial reduction greater than 40% in the frequency of needle and syringe sharing for a notable decrease in the prevalence of HCV and HIV to be observed over a ten year period if all addicts are reached.

1.11.2 Models that Examine the Spread of HCV amongst Injecting Drug Users

Many authors studied the prevalence of HCV amongst injecting drug users through the sharing of needles and syringes. In 2007, Vickerman modeled the impact on HCV transmission of reducing syringe sharing: the London case study (Vickerman et al., 2007). Later, Vickerman et al. (2012b) present a study to understand the trend of HCV/HIV prevalence amongst injecting drug users. Moreover, Corson et al. (2013) model the transmission of HCV according to time since onset of injection, where the population can be separated into two risk groups (naive and experienced) with different injecting risk behaviours. In a recent study, Grebely & Dore (2014) discussed the eradication of HCV infection in injecting drug users which is defined as the complete and permanent worldwide reduction to zero new cases through deliberate efforts, with no further control measures required. In this section we review two models, which approximate the spread of HCV, as they are the most relevant to our work. The first one is by Vickerman et al. (2007), and the second one is by Corson et al. (2012).

The model of Vickerman et al. (2007)

Vickerman et al. (2007) used a deterministic compartmental model to describe the transmission of HCV amongst London injecting drug users for 2002 - 2003. This work simulated the dynamics of HCV infection over the length of injecting career of the addicts and was used to explore the impact of intervention measures that reduced needle sharing in all addicts, addicts who have been sharing needles for more than one year, and addicts with low or high frequencies of needle sharing. In this model, the transmission of HCV through the sharing of injecting paraphernalia and the sexual transmission of HCV was not considered. The model structure allowed for two acute HCV infectious classes, one for those addicts who could spontaneously resolve their acute infection and one which allowed addicts to progress to the chronic stage of infection. The inclusion of these two separate acute HCV infectious classes meant that the authors could assign a different transmission probability for each acute class.

Vickerman et al. divided the addicts' population into three behavioural subgroups depending on their needle sharing frequency, to stratify the population by HCV infection status. Therefore, the population of addicts is separated into those that do not share needles, those who share needles infrequently and those who frequently share needles. Addicts in the low and high risk groups were allowed to mix to form sharing partnerships and it was possible to vary the degree of mixing between random mixing and assortative mixing.

Model results showed that large sustained reductions in sharing rates (greater

than 50%) would reduce HCV seroprevalence in addicts injecting for more than eight years and modest reductions (less than 25%) would reduce HCV in those addicts injecting for less than four years. To reduce HCV prevalence to less than 10% the simulations showed that needle sharing rates would have to reduce from the baseline estimate of 16 events per month to 1 - 2 events per month. Furthermore, the model results also suggested large reductions in HCV seroprevalence would only be achieved if interventions were aimed at all addicts and reached them within their first year of injecting. This modelling work provided insights into the difficulties in controlling the spread of HCV amongst injecting drug users and the importance of ensuring that interventions to reduce needle sharing reached all addicts, including those who are within their first year of injecting. However, these projections assumed that the reduction in needle sharing is maintained over the course of the injecting careers of the injecting drug users.

The model by Corson et al. (2012)

Corson et al. developed a deterministic, compartmental mathematical model to approximate the transmission of HCV among injecting drug users, building on the model developed by Vickerman et al. (2007). They aimed to determine the level of needle sharing, needle cleaning and needle exchange necessary for HCV elimination among injecting drug users in Glasgow. The structure of the model enables addicts to progress through various stages of HCV infection. The population of addicts is divided into those susceptible to HCV infection denoted x, for those not previously infected, and x_1 for previously infected. Those in the acute stage of HCV infection

(h_1 and h_2), those who have progressed to the chronic stage of HCV infection y and those immune to HCV reinfection z (see Figure 1.2). The force of infection experienced by a single susceptible IDU is given by $f = \lambda(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y)$. Then the authors derived a system of nine differential equations, six of them describe the transmission of HCV among addicts and three describe HCV prevalence in needles.

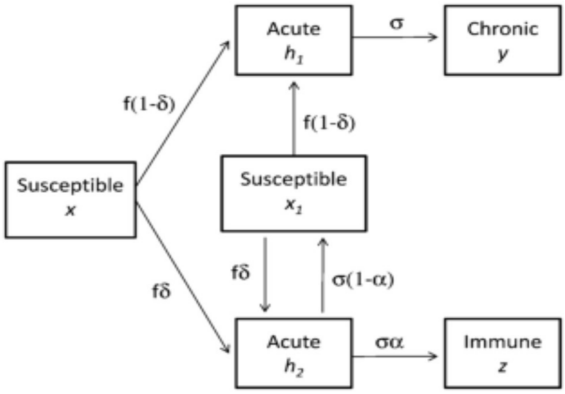


Figure 1.2: HCV transmission flow diagram. The arrows indicate the possible transitions for addicts between stages of HCV infection and the parameters shown are the per capita rate of flow between the stages (taken from Corson et al. (2012)).

Parameter	Definition
ϕ	Probability of successful needle cleaning.
τ	Needle turnover rate.
λ	Needle sharing rate.
α_h	Acute HCV transmission probability.
α_y	Chronic HCV transmission probability.
$1/\sigma$	Duration of the acute HCV phase.
μ	Rate of joining and leaving sharing, injecting population per addict.
δ	Proportion that resolve HCV infection.
α	Proportion of addicts that become immune.

Table 1.3: Table of Corson et al. (2012) model parameters definition.

Then they looked at the basic reproductive number R_0 which determines the general behaviour of HCV among addicts and needles. For this model, the expression of the

total number of secondary infections caused by a single infectious addict entering the DFE is given by:

$$R_0 = \frac{\lambda(1-\phi)}{\mu(\mu+\sigma)(1+\hat{\tau})[\mu\alpha_h + \alpha_y\sigma(1-\delta)]},$$

where the parameters are defined in Table 1.3, $\gamma = n/m$ is the number of addicts per needle in the population and $\hat{\tau} = \tau/\lambda\gamma$. The main theorem of this model, states that if $R_0 \leq 1$ the model has a unique equilibrium solution where HCV has died out in both addicts and needles. If $R_0 > 1$, there is still the disease-free equilibrium, however there is also a unique endemic equilibrium. Then, Corson et al. simulated HCV for the population of Glasgow injecting drug users over time. The model parameters are estimated and they examine the behaviour of HCV when $R_0 \leq 1$ and $R_0 > 1$. Simulation has shown that the model tends to the endemic equilibrium value with realistic parameter values giving HCV prevalence estimated at 69% which agrees with observed data. Moreover, the authors examined the impact of various control measures on R_0. In particular they determined the threshold values of needle sharing, needle cleaning and needle turnover that lead to R_0 less than unity and HCV elimination in addicts and needles.

1.12 Conclusion

The results of a literature review of the epidemiology and modelling of HCV, as well as a more general overview of the concepts used to model infectious diseases have been presented in this chapter. HCV causes substantial morbidity and mortality, and is easily transmitted through contaminated syringes. This virus is primarily

transmitted through blood to blood contact, with the majority of infections in developed countries attributed to a history of injecting drug use (Aceijas & Rhodes, 2007). Nevertheless, other routes such as sexual, perinatal transmission, tattooing, acupuncture and intranasal drug use are likely for possible transmission (Tajima & Sonoda, 1996; Jafari et al., 2010; Tohme & Holmberg, 2010; WHO, 2013). There is no vaccine to protect against infection, but antiviral treatment is available for those with chronic HCV. Although the success of treatment is genotype specific, the overall response rate to treatment is 50 - 60% (Fried et al., 2002).

The mathematical models used to understand, forecast and control the spread of infectious diseases such as HCV are diverse and growing rapidly. Also, these models are used to understand the transmission of infections and to evaluate the potential impact of control programmes in reducing morbidity and mortality. Thus, we outlined the model structure and discussed the basic reproductive number R_0 as the fundamental parameter which determines the disease dynamic and behaviour.

Heterogeneity is the primary complexity complicating model structure, both between individuals in terms of risk of infection from other members of the population and in pathogens. This is an area of active research in infectious diseases epidemiology that is focused on a variety of potentially important problems (Dowdle & Hopkins, 1998; Farrington et al., 2013). In order to prevent the prevalence of HCV, harm reduction policies and their impacts are discussed. In general, there is good evidence that the full harm reduction NSPs plus OST can substantially reduce the risk of HCV transmission among injecting drug users (Martin et al., 2011; Turner

et al., 2011; Vickerman et al., 2012a).

In the next chapter we shall develop accurate models of the spread of HCV and discuss a mathematical model of the heterogeneity impact of the spread of HCV among addicts and needles. It will look at the model hypotheses and the model governing system of differential equations that describe the progress of HCV.

Chapter 2

Modelling the Effects of Heterogeneity on the Spread of HCV

In this chapter we shall study and set up a deterministic mathematical model of the effects of heterogeneity on the spread of HCV amongst injecting drug users and shooting galleries. The first section of this chapter discusses the set of hypotheses which are assumed to govern the system of differential equations that describe the spread of HCV. Then we move on to give an expression of the key parameter of this model "the basic reproductive number" R_0. We finish this section by giving some special scenarios of assumptions of different parameters that minimise R_0. Eventually, a brief summary and discussion conclude.

We develop a mathematical model of the prevalence of HCV amongst a population of injecting drug users sharing needles in shooting galleries, based on the simple model that was discussed by Corson et al. (2012) which assumed homogeneity in time since onset of injection and needle sharing rates, and a model of

Greenhalgh (1996) who studied the effects of heterogeneity on the spread of HIV and AIDS among a population of injecting drug users. Compared with the model by Corson et al. (2012), this model focusses on the impact of heterogeneity on the prevalence of HCV among this risky group. Furthermore, we do not consider the treatment of chronically infected injecting drug users with antiviral therapy. Now, we shall describe the set of hypotheses that are used to set up our model, then derive the model equations.

2.1 Hypotheses and Notation

We consider a population of n injecting drug addicts divided into p groups sizes $n_1, n_2, \ldots, n_p$ where $n = \sum_{i=1}^{p} n_i$ and n is large and constant for all time t. Each group is homogeneous and differs from other groups, for example: female and male or high sharing, low sharing and never sharing needles. In this model, we assume that addicts stay in the same group for all time until he or she dies or stops injecting the drug. As a result, when addicts leave the population due to permanent cessation of injecting behaviour or death at per capita μ, they will immediately be replaced at the same rate by other addicts susceptible to HCV infection. Later in Chapter Seven we will develop this model by assuming that addicts are allowed to move in and out of groups. Moreover, there are q shooting galleries, and the number of needles in shooting gallery j is m_j where $m = \sum_{j=1}^{q} m_j$ and m is large and constant for all time t. Each type i drug addict visits shooting galleries at rate λ_i.

On each visit he or she chooses shooting gallery j with probability P_{ij} for $j = 1, 2 \ldots q$ where $P_{ij} \geq 0$ and $\sum_{j=1}^{q} P_{ij} = 1$. On each visit to a shooting gallery the

addict injects once with a needle chosen at random from that shooting gallery. When an addict of type i leaves the population due to either permanent cessation of injecting behavior or death, at per capita rate μ, he or she is replaced immediately by an addict susceptible to HCV infection. The arrival rate of type i addicts at a given needle in shooting gallery j is $\Lambda_{ij} = (\lambda_i n_i P_{ij}/m_j)$. This model considers a heterogeneous population of drug users. We aim to approximate the spread of HCV in the population, where this population is divided into p groups labeled $i = 1, 2, \ldots, p$. The ith group is also divided into six different stages as follows (see Figure 1.2):

1. we denote by x_i the addicts who have never been infected with HCV and are susceptible to HCV through sharing needles.

2. we denote by x_{1i} the addicts who have been previously infected and have recovered and are susceptible to HCV infection again through sharing needles.

3. we denote by h_{1i} those in the acute stage of HCV infection which leads to chronic infection.

4. we denote by h_{2i} those in the acute stage of HCV infection which leads to self limiting HCV infection.

5. we denote by y_i those whom have progressed to the chronic stage of HCV infection.

6. we denote by z_i those immune to HCV re-infection.

Similarly, the shooting galleries are divided into q groups labeled $j = 1, 2, \ldots, q$. Each shooting gallery j contains three different type of infectious needles divided as follows:

1. we denote by h_{1j} the needles which were last used by an addict in the h_1 acute stage of HCV infection.

2. we denote by h_{2j} the needles which were last used by an addict in the h_2 acute stage of HCV infection.

3. we denote by y_j the needles which were last used by an addict in the y chronic stage of HCV infection.

Also, in this model we assume that:

- The average rate that a type i addict shares needles is denoted by λ_i.

- A type i addict in shooting gallery j cleans his or her needle prior to use with probability ϕ_{ij}.

- The transmission probability relating to acute and chronic HCV infection by shared needles is denoted by α_h and α_y respectively.

- A susceptible addict of type i (either x_i or x_{1i}) once infected with HCV will progress to the acute stage of infection (either h_{1i} or h_{2i}). Those newly infected with HCV will progress to the acute stage h_{1i} with probability $(1-\delta)$. From here these addicts will either die, leave the sharing injecting population or progress to the chronic infection and remain there until they either die or leave the sharing injecting population. The remaining proportion δ of newly infected type i infected addicts progress to the acute h_{2i} stage. From here these addicts will either die, leave the sharing injecting population or progress. Of those that progress a fraction α progress to the immune stage, where they then remain until they either die or leave the sharing injecting population. The remaining fraction $(1-\alpha)$ of those who progress return to the susceptible class.

- The only way that a type i addict can be infected is through the sharing of needles used by a HCV acutely or chronically infected addict. Moreover, the infectivity of the last addict who used the needle determines the infectivity of this needle. Thus a needle last used by a susceptible addict is left uninfectious, a needle last used by an addict in the acute h_1 stage of infectivity is left in the h_1 stage (transmission probability per injection α_h), a needle last used by an addict in the acute h_2 stage of infectivity is left in the h_2 stage (transmission probability per injection α_h) and a needle last used by an addict in the chronic y stage of infectivity is left in the y stage (transmission probability per injection α_y).

- The average duration that a type i addict remains in the acute stage is $1/\sigma$ time units.

- The addict population is of size n where n is large and constant. Therefore, any addicts who leave the population (e.g. due to death, entry to treatment programmes, or incarceration or other reasons) are immediately replaced by susceptible addicts. The per capita rate at which addicts leave or enter the population is denoted by μ.

- We assume a needle turnover rate (the average rate at which addicts change their needles for clean needles in shooting gallery j) of τ_j per year, addicts can become infected only through the sharing of needles used by an HCV acutely or chronically infected addict and that infectious needles do not lose their infectivity if they are left unused for a period of time. An infectious needle, when used by a susceptible, becomes non-infectious.

2.2 Governing Model Equations

Let $\pi_{xi}(t)$ and $\pi_{x_1i}(t)$ denote respectively the fraction of addicts in x_i-susceptible and x_{1i}-susceptible stages of type i at time t. Using a similar definition, $\pi_{h_1i}(t)$ and $\pi_{h_2i}(t)$ denote respectively the fractions of addicts of a type i in the acute stages h_1 and h_2 at time t. $\pi_{yi}(t)$ and $\pi_{zi}(t)$ denote respectively the fractions of addicts of a type i in the chronic and immune stages at time t. In the same way, $\beta_{h_1j}(t), \beta_{h_2j}(t)$ and $\beta_{yj}(t)$ denote respectively the fractions of needles at time t in shooting gallery j that were last used by an infected addict in infectious state h_1, h_2 and y respectively. Also denote by $\gamma = n/m$, the number of addicts per needle in the population. Note that in this model, the parameter μ is both the per capita birth rate and the per capita death rate for all addicts.

The number of type i x_i-susceptible addicts at time $t + \Delta t$

= The number of type i x_i-susceptible addicts at time t

\+ the number of type i x_i-susceptible addicts recruited to share intravenous injecting equipments in $[t, t + \Delta t)$

− the number of type i x_i-susceptible addicts who develop acute HCV infection as type i addicts choosing shooting gallery j in $[t, t + \Delta t)$ for some $j = 1, 2, \ldots q$.

− the number of type i x_i-susceptible addicts who leave the population due cessation of injecting drug use or death in $[t, t + \Delta t)$.

We write this equation mathematically as follows:

$$\begin{aligned} n\pi_{xi}(t+\Delta t) &= n\pi_{xi}(t) + n\mu\Delta t - \sum_{j=1}^{q} n\pi_{xi}(t)\Delta t\lambda_i P_{ij}(1-\phi_{ij}) \\ &\quad (\alpha_h(\beta_{h_1 j}(t) + \beta_{h_2 j}(t)) + \alpha_y\beta_{yj}(t)) - n\pi_{xi}(t)\mu\Delta t + o(\Delta t). \end{aligned}$$

Subtracting $n\pi_{xi}(t)$ from the two sides, we deduce that:

$$\begin{aligned} n\pi_{xi}(t+\Delta t) - n\pi_{xi}(t) &= n\mu\Delta t - \sum_{j=1}^{q} n\pi_{xi}(t)\Delta t\lambda_i P_{ij}(1-\phi_{ij}) \\ &\quad (\alpha_h(\beta_{h_1 j}(t) + \beta_{h_2 j}(t)) + \alpha_y\beta_{yj}(t)) - n\pi_{xi}(t)\mu\Delta t + o(\Delta t). \end{aligned}$$

Dividing by $n\Delta t$ and letting $\Delta t \longrightarrow 0$ gives the following:

$$\frac{d\pi_{xi}}{dt} = \mu - \mu\pi_{xi} - \pi_{xi}\sum_{j=1}^{q} \lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j} + \beta_{h_2 j}) + \alpha_y\beta_{yj}\big).$$

Similarly, the number of type i x_{1i}-susceptible addicts at time $t+\Delta t$

$=$ the number of type i x_{1i}-susceptible addicts at time t

$+$ the number of type i h_{2i} infected addicts that spontaneously resolve an HCV infection in time $[t, t+\Delta t)$

$-$ the number of type i x_{1i}-susceptible addicts who develop acute HCV infection as type i addicts choosing shooting gallery j in $[t, t+\Delta t)$ for some $j = 1, 2, \ldots q$

$-$ the number of type i x_{1i}-susceptible addicts who leave the population due to cessation of injecting drug use or death in $[t, t+\Delta t)$.

Mathematically this can be written as:

$$\begin{aligned} n\pi_{x_1 i}(t+\Delta t) &= n\pi_{x_1 i}(t) + \sigma(1-\alpha)n\pi_{h_2 i}(t)\Delta t - \sum_{j=1}^{q} n\pi_{x_1 i}(t)\Delta t\lambda_i P_{ij}(1-\phi_{ij}) \\ &\quad (\alpha_h(\beta_{h_1 j}(t)+\beta_{h_2 j}(t)) + \alpha_y\beta_{yj}(t)) - n\pi_{x_1 i}(t)\mu\Delta t + o(\Delta t). \end{aligned}$$

Subtracting $n\pi_{x_1 i}(t)$ from the two sides, we deduce that:

$$\begin{aligned} n\pi_{x_1 i}(t+\Delta t) - n\pi_{x_1 i}(t) &= \sigma(1-\alpha)n\pi_{h_2 i}(t)\Delta t - \sum_{j=1}^{q} n\pi_{x_1 i}(t)\Delta t\lambda_i P_{ij}(1-\phi_{ij}) \\ &\quad (\alpha_h(\beta_{h_1 j}(t)+\beta_{h_2 j}(t)) + \alpha_y\beta_{yj}(t)) - n\pi_{x_1 i}(t)\mu\Delta t + o(\Delta t). \end{aligned}$$

Dividing by $n\Delta t$ and letting $\Delta t \longrightarrow 0$ gives the following:

$$\frac{d\pi_{x_1 i}}{dt} = \sigma(1-\alpha)\pi_{h_2 i} - \mu\pi_{x_1 i} - \pi_{x_1 i}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j}) + \alpha_y\beta_{yj}\big).$$

The number of type i acute infected h_{1i} addicts at time $t+\Delta t$

$=$ the number of type i acute h_{1i} infected addicts at time t

$+$ the number of type i susceptible addicts (both x_i and x_{1i}) who develop type i acute h_{1i} HCV infection in time $[t, t+\Delta t)$

$-$ the number of type i acute h_{1i} addicts who develop chronic HCV infection in $[t, t+\Delta t)$

$-$ the number of type i acute h_{1i} addicts who leave the population due to cessation of injecting drug use or death in $[t, t+\Delta t)$.

Mathematically this can be written as:

$$\begin{aligned} n\pi_{h_1 i}(t+\Delta t) &= n\pi_{h_1 i}(t) + \sum_{j=1}^{q} n\Delta t\lambda_i P_{ij}(1-\delta)\Big(\pi_{x_i}(t) + \pi_{x_1 i}(t)\Big)(1-\phi_{ij}) \\ &\quad (\alpha_h(\beta_{h_1 j}(t) + \beta_{h_2 j}(t)) + \alpha_y\beta_{yj}(t)) - (\mu+\sigma)n\pi_{h_1 i}(t)\Delta t + o(\Delta t). \end{aligned}$$

As we did earlier, subtracting $n\pi_{h_1 i}(t)$ from the two sides, dividing by $n\Delta t$ and letting $\Delta t \longrightarrow 0$ gives the following:

$$\begin{aligned} \frac{d\pi_{h_1 i}}{dt} &= \sum_{j=1}^{q}(1-\delta)(\pi_{xi} + \pi_{x_1 i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j} + \beta_{h_2 j}) + \alpha_y\beta_{yj}\big) \\ &\quad - (\mu+\sigma)\pi_{h1i}. \end{aligned}$$

We use the same argument to calculate the number of type i acute infected h_{2i} addicts at time $t + \Delta t$.

So, the number of type i acute infected h_{2i} addicts at time $t + \Delta t$

= the number of type i acute h_{2i} infected addicts at time t

\+ the number of type i susceptible addicts (both x_i and x_{1i}) who develop type i acute h_{2i} HCV infection in $[t, t + \Delta t)$

− the number of type i acute h_{2i} addicts who resolve the infection or develop to the immune class in $[t, t + \Delta t)$

− the number of type i of acute h_{2i} addicts who leave the population due to cessation of injecting drug use or death in $[t, t + \Delta t)$.

Mathematically this can be written as:

$$\begin{aligned} n\pi_{h_2 i}(t+\Delta t) &= n\pi_{h_2 i}(t) + \sum_{j=1}^{q} n\Delta t\lambda_i P_{ij}\delta\Big(\pi_{x_i}(t) + \pi_{x_1 i}(t)\Big)(1-\phi_{ij}) \\ & \quad (\alpha_h(\beta_{h_1 j}(t) + \beta_{h_2 j}(t)) + \alpha_y\beta_{yj}(t)) - (\mu+\sigma)n\pi_{h_2 i}(t)\Delta t + o(\Delta t). \end{aligned}$$

Subtracting $n\pi_{h_2 i}(t)$ from the two sides, dividing by $n\Delta t$ and letting $\Delta t \longrightarrow 0$ gives the following:

$$\frac{d\pi_{h_2 i}}{dt} = \sum_{j=1}^{q} \delta(\pi_{xi} + \pi_{x_1 i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j} + \beta_{h_2 j}) + \alpha_y\beta_{yj}\big) - (\mu+\sigma)\pi_{h_2 i}.$$

The number of type i chronic infected y_i addicts at time $t + \Delta t$

$=$ the number of type i chronic y_i infected addicts at t

$+$ the number of type i acute h_{1i} infected addicts who develop chronic y_i infection HCV time in $[t, t+\Delta t)$

$-$ the number of type i chronic y_i addicts who leave the population due to cessation of injecting drug use or death in $[t, t+\Delta t)$.

Thus we have:

$$n\pi_{y_i}(t+\Delta t) = n\pi_{y_i}(t) + n(\pi_{h1_i}(t)\sigma - \mu\pi_{y_i}(t))\Delta t + o(\Delta t).$$

Subtracting $n\pi_{y_i}(t)$ from the two sides, dividing by $n\Delta t$ and letting $\Delta t \longrightarrow 0$ gives the following:

$$\frac{d\pi_{yi}}{dt} = \sigma\pi_{h_1 i} - \mu\pi_{yi}.$$

To calculate the last equation of the addicts model, we use a similar method for type i immune addicts z_i. We deduce that:

$$\frac{d\pi_{zi}}{dt} = \sigma\alpha\pi_{h_2 i} - \mu\pi_{zi}.$$

The number of type j of acute infected h_{1j} needles at time $t + \Delta t$

$=$ the number of type j acute h_{1j} infected needles at t

$+$ the number of non-acute h_{1j} infected needles which are used by type j acute h_{1i} infected addicts in $[t, t + \Delta t)$ for $i = 1, 2, \ldots p$

$-$ the number of type j acute h_{1j} needles which are used by non-acute h_{1i} addicts in $[t, t + \Delta t)$ for $i = 1, 2, \ldots p$

$-$ the number of type j acute h_{1j} needles which are exchanged in shooting gallery j in $[t, t + \Delta t)$.

Mathematically, we can write this as:

$$\begin{aligned} m\beta_{h_1 j}(t + \Delta t) &= m\beta_{h_1 j}(t) + m\sum_{i=1}^{p} \Lambda_{ij}\pi_{h_1 i}(t)(1 - \beta_{h_1 j}(t))\Delta t \\ &\quad -m\beta_{h_1 j}(t)\sum_{i=1}^{p} \Lambda_{ij}(1 - \pi_{h_1 i}(t))\Delta t - m\tau_j\beta_{h_1 j}(t).\Delta t + o(\Delta t). \end{aligned}$$

Subtracting $m\beta_{h_1 j}(t)$ from the two sides, dividing by $m\Delta t$ and letting $\Delta t \longrightarrow 0$ gives the following:

$$\frac{d\beta_{h_1 j}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_1 i}(1 - \beta_{h_1 j}) - \beta_{h_1 j}\sum_{i=1}^{p} \Lambda_{ij}(1 - \pi_{h_1 i}) - \tau_j\beta_{h_1 j}.$$

We use a similar method to calculate the rate of change of the number of type j acute h_{2j} and chronic y_j infected needles respectively, at time t, to deduce the following:

$$\frac{d\beta_{h_2j}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_2i}(1-\beta_{h_2j}) - \beta_{h_2j}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{h_2i}) - \tau_j\beta_{h_2j},$$

and

$$\frac{d\beta_{yj}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{yi}(1-\beta_{yj}) - \beta_{yj}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{yi}) - \tau_j\beta_{yj}.$$

The system of differential equations which describe the progress of the disease are:

$$\frac{d\pi_{xi}}{dt} = \mu - \mu\pi_{xi} - \pi_{xi}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1j}+\beta_{h_2j}) + \alpha_y\beta_{yj}\big), \tag{2.1}$$

$$\frac{d\pi_{x_1i}}{dt} = \sigma(1-\alpha)\pi_{h_2i} - \mu\pi_{x_1i} - \pi_{x_1i}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1j}+\beta_{h_2j}) + \alpha_y\beta_{yj}\big), \tag{2.2}$$

$$\frac{d\pi_{h_1i}}{dt} = \sum_{j=1}^{q}(1-\delta)(\pi_{xi}+\pi_{x_1i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1j}+\beta_{h_2j}) + \alpha_y\beta_{yj}\big) - (\mu+\sigma)\pi_{h_1i}, \tag{2.3}$$

$$\frac{d\pi_{h_2i}}{dt} = \sum_{j=1}^{q}\delta(\pi_{xi}+\pi_{x_1i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1j}+\beta_{h_2j}) + \alpha_y\beta_{yj}\big) - (\mu+\sigma)\pi_{h_2i}, \tag{2.4}$$

$$\frac{d\pi_{yi}}{dt} = \sigma\pi_{h_1i} - \mu\pi_{yi}, \tag{2.5}$$

$$\frac{d\pi_{zi}}{dt} = \sigma\alpha\pi_{h_2i} - \mu\pi_{zi}, \tag{2.6}$$

$$\frac{d\beta_{h_1j}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_1i}(1-\beta_{h_1j}) - \beta_{h_1j}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{h_1i}) - \tau_j\beta_{h_1j}, \tag{2.7}$$

$$\frac{d\beta_{h_2j}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_2i}(1-\beta_{h_2j}) - \beta_{h_2j}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{h_2i}) - \tau_j\beta_{h_2j}, \tag{2.8}$$

$$\frac{d\beta_{yj}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{yi}(1-\beta_{yj}) - \beta_{yj}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{yi}) - \tau_j\beta_{yj}, \tag{2.9}$$

with suitable initial conditions: $\pi_{xi}(0), \pi_{x_1 i}(0), \pi_{h_1 i}(0), \pi_{h_2 i}(0), \pi_{yi}(0), \pi_{zi}(0), \beta_{h_1 j}(0)$, $\beta_{h_2 j}(0)$ and $\beta_{yj}(0) \geq 0$ and $\pi_{xi}(0) + \pi_{x_1 i}(0) + \pi_{h_1 i}(0) + \pi_{h_2 i}(0) + \pi_{yi}(0) + \pi_{zi}(0) = 1$. Correspondingly, $\beta_{h_1 j}(0) + \beta_{h_2 j}(0) + \beta_{yj}(0) \leq 1$. The model equations (2.1) to (2.6) govern the progress of the spread of HCV amongst injecting drug users in each group i of addicts over time while equations (2.7) to (2.9) illustrate how the proportion of infectious needles change over time in each shooting gallery j. Now we move on to compute the key parameter of our model, the basic reproductive number.

2.3 The Basic Reproductive Number

The basic reproductive number R_0, is known as a central quantity in the investigation and management of infectious disease (Dietz, 1993). This value is defined as the expected number of secondary cases caused by a single newly infected individual entering a completely disease-free population at equilibrium (Diekmann et al., 1990). In this definition a secondary case means a case caused by direct contact with the initial infected case. In our case a secondary case means: an addict infected via sharing a needle with an initially infected individual entering the disease-free population at equilibrium. In this section, we shall derive an expression for R_0 as there are multiple types of infected addicts and needles. The importance of this key parameter is that it is a determinant of the total behaviour of our heterogeneous model for the progress of HCV among addicts and needles over time.

The infection scenario can be as follows: (1) the infected addict of type i passes the infection to uninfected needles in shooting gallery j, (2) the newly infected needles (at any stage of infectivity) then infect susceptible addicts of type k. To derive

this number we first consider a single newly infected addict of type i entering a disease-free population containing only susceptible addicts (at equilibrium).

By our assumption all rates are constant, this means that the expected duration (time) of infection is the inverse of the removal rate. Thus, each infected addict shares injecting needles for an average $1/(\mu+\sigma)$ time units. During this time he or she uses needles at rate λ_i and chooses the shooting gallery j at probability P_{ij}, and once infected with HCV moves into the acute stage h_{1i} with probability $(1-\delta)$. In this case, they remain there for an average $1/(\mu+\sigma)$ time units. They then progress to the chronic stage of infection with probability $\sigma/(\mu+\sigma)$ where they remain for an average $1/\mu$ time units, otherwise they leave the population. This addict, once infected, can also move into the acute stage h_{2i} with probability δ. They remain there for an average $1/(\mu+\sigma)$ time units. After, there are two stages which addicts can progress to, the immune stage with probability $\sigma\alpha/(\mu+\sigma)$ and they remain there for an average $1/\mu$ time units, or the x_{1i}-susceptible stage with probability $\sigma(1-\alpha)/(\mu+\sigma)$ where they remain for an average $1/\mu$ time units, otherwise they leave the population. Hence, in total a single newly infected addict in group i causes:

$$\frac{\lambda_i P_{ij}(1-\delta)}{\mu+\sigma} \qquad \text{acute } h_{1j} \text{ infectious needles,} \tag{2.10}$$

$$\frac{\lambda_i P_{ij}\delta}{\mu+\sigma} \qquad \text{acute } h_{2j} \text{ infectious needles,} \tag{2.11}$$

and

$$\frac{\lambda_i P_{ij}\sigma(1-\delta)}{\mu(\mu+\sigma)} \qquad \text{chronic } y_j \text{ infectious needles,} \tag{2.12}$$

in shooting gallery j. We assume that these newly infected needles will be used by uninfected addicts of different groups k. Thus, we want to derive the expected number of these addicts in group k infected by these newly infected needles. The acute h_{1j} needle is infected for $1/(\sum_{l=1}^{p} \Lambda_{lj} + \tau_j)$ time units. During this time it infects:

$$\frac{\Lambda_{kj}(1-\phi_{kj})\alpha_h}{\sum_{l=1}^{p} \Lambda_{lj} + \tau_j} \qquad \text{addicts in group } k. \tag{2.13}$$

Similarly, a single needle last used and infected by an addict in class h_{2j} entering a disease-free population at equilibrium infects:

$$\frac{\Lambda_{kj}(1-\phi_{kj})\alpha_h}{\sum_{l=1}^{p} \Lambda_{lj} + \tau_j} \qquad \text{addicts in group } k, \tag{2.14}$$

and a single needle last used and infected by an addict in class y_j entering a disease-free population at equilibrium infects:

$$\frac{\Lambda_{kj}(1-\phi_{kj})\alpha_y}{\sum_{l=1}^{p} \Lambda_{lj} + \tau_j} \qquad \text{addicts in group } k. \tag{2.15}$$

Thus, Q_{ik} the total expected number of secondary addicts in group k left infected by a single newly infected addict entering group i is the sum of those infected by h_{1j} needles plus the sum of those infected by h_{2j} needles plus the sum of those infected via y_j needles. So

$$\begin{aligned} Q_{ik} \;=\; \sum_{j=1}^{q} \Bigg(& \frac{\lambda_i P_{ij}(1-\delta)}{\mu+\sigma} \cdot \frac{\Lambda_{kj}(1-\phi_{kj})\alpha_h}{\sum_{e=1}^{p} \Lambda_{ej} + \tau_j} \\ & + \frac{\lambda_i P_{ij}\delta}{\mu+\sigma} \cdot \frac{\Lambda_{kj}(1-\phi_{kj})\alpha_h}{\sum_{e=1}^{p} \Lambda_{ej} + \tau_j} \\ & + \frac{\lambda_i P_{ij}\sigma(1-\delta)}{\mu(\mu+\sigma)} \cdot \frac{\Lambda_{kj}(1-\phi_{kj})\alpha_y}{\sum_{e=1}^{p} \Lambda_{ej} + \tau_j} \Bigg), \end{aligned}$$

$$= \xi \sum_{j=1}^{q} \frac{\lambda_i P_{ij} \Lambda_{kj} (1 - \phi_{kj})}{\sum_{e=1}^{p} \Lambda_{ej} + \tau_j}, \tag{2.16}$$

where $\xi = (\alpha_y \sigma(1-\delta) + \alpha_h \mu)/\mu(\mu + \sigma)$.

Similarly, if we consider a newly infected needle entering shooting gallery j at the disease-free equilibrium (containing only uninfected needles), there are three possibilities. The needle must either be a type h_{1j}, h_{2j} or y_j infected needle in shooting gallery j. The expected number of addicts infected in addicts group k are again given in the formulae (2.13), (2.14) and (2.15) respectively in each of the three cases. Then the expected number of needles infected in shooting gallery r are given by the formulae (2.10), (2.11) and (2.12) with i replaced by k and j replaced by r,

$$\frac{\lambda_k P_{kr}(1-\delta)}{\mu + \sigma} \qquad \text{acute } h_{1r} \text{ infectious needles,}$$

$$\frac{\lambda_k P_{kr}\delta}{\mu + \sigma} \qquad \text{acute } h_{2r} \text{ infectious needles,}$$

and

$$\frac{\lambda_k P_{kr}\sigma(1-\delta)}{\mu(\mu + \sigma)} \qquad \text{chronic } y_r \text{ infectious needles.}$$

Thus the $3q \times 3q$ matrix $\mathbf{M}$ giving the expected number of type h_{1r}, h_{2r} and y_r infected needles in shooting gallery r caused by a single h_{1j}, h_{2j} and y_j infected needle entering the disease-free equilibrium in shooting gallery j is given by a matrix in blocks such as

$$\begin{array}{c} \\ h_{1j} \\ h_{2j} \\ y_j \end{array} \begin{array}{c} \begin{array}{ccc} h_{1r} & h_{2r} & y_r \end{array} \\ \begin{pmatrix} X_{jr}\frac{(1-\delta)\alpha_h}{\mu+\sigma} & X_{jr}\frac{\delta\alpha_h}{\mu+\sigma} & X_{jr}\frac{\sigma(1-\delta)\alpha_h}{\mu(\mu+\sigma)} \\ X_{jr}\frac{(1-\delta)\alpha_h}{\mu+\sigma} & X_{jr}\frac{\delta\alpha_h}{\mu+\sigma} & X_{jr}\frac{\sigma(1-\delta)\alpha_h}{\mu(\mu+\sigma)} \\ X_{jr}\frac{(1-\delta)\alpha_y}{\mu+\sigma} & X_{jr}\frac{\delta\alpha_y}{\mu+\sigma} & X_{jr}\frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\sigma)} \end{pmatrix} \end{array}$$

where

$$X_{jr} = \sum_{k=1}^{p} \frac{\Lambda_{kj}(1-\phi_{kj})\lambda_k P_{kr}}{\sum_{e=1}^{p}\Lambda_{ej}+\tau_j}.$$

We assert that the matrix $\mathbf{M}$ has spectral radius:

$$\rho(\mathbf{M}) = \xi\rho(\mathbf{X}),$$

where $\xi = (\alpha_y\sigma(1-\delta)+\alpha_h\mu)/\mu(\mu+\sigma)$ as before and ρ denotes the spectral radius. In the case $q = 1$ this is straightforward as then the matrix is

$$X_{11}a_I b_J \qquad \text{for} \quad I, J = 1, 2, 3$$

where

$$a_1 = a_2 = \alpha_h, \quad a_3 = \alpha_y, \quad b_1 = \frac{(1-\delta)}{\mu+\sigma}, \quad b_2 = \frac{\delta}{\mu+\sigma} \quad \text{and} \quad b_3 = \frac{\sigma(1-\delta)}{\mu(\mu+\sigma)}.$$

In this case (a proportional mixing matrix) the characteristic equation is

$$0 = \det \begin{vmatrix} X_{11}a_1b_1-\omega & X_{11}a_1b_2 & X_{11}a_1b_3 \\ X_{11}a_2b_1 & X_{11}a_2b_2-\omega & X_{11}a_2b_3 \\ X_{11}a_3b_1 & X_{11}a_3b_2 & X_{11}a_3b_3-\omega \end{vmatrix}$$

i.e.

$$(X_{11}a_1b_1-\omega)(X_{11}a_2b_2-\omega)(X_{11}a_3b_3-\omega)+2X_{11}^3a_1a_2a_3b_1b_2b_3$$
$$-(X_{11}a_1b_1-\omega)X_{11}^2a_2a_3b_2b_3-(X_{11}a_2b_2-\omega)X_{11}^2a_1a_3b_1b_3$$
$$-(X_{11}a_3b_3-\omega)X_{11}^2a_1a_2b_1b_2=0.$$

So, the roots are $\omega=0,\omega=0$ and $\omega=tr(\mathbf{M})=X_{11}(a_1b_1+a_2b_2+a_3b_3)=\xi X_{11}=\xi\rho(\mathbf{X})$ as required.

In the case $q=2$ the characteristic equation is:

$$0=\det\begin{vmatrix} X_{11}a_1b_1-\omega & X_{11}a_1b_2 & X_{11}a_1b_3 & X_{12}a_1b_1 & X_{12}a_1b_2 & X_{12}a_1b_3\\ X_{11}a_2b_1 & X_{11}a_2b_2-\omega & X_{11}a_2b_3 & X_{12}a_2b_1 & X_{12}a_2b_2 & X_{12}a_2b_3\\ X_{11}a_3b_1 & X_{11}a_3b_2 & X_{11}a_3b_3-\omega & X_{12}a_3b_1 & X_{12}a_3b_2 & X_{12}a_3b_3\\ X_{21}a_1b_1 & X_{21}a_1b_2 & X_{21}a_1b_3 & X_{22}a_1b_1-\omega & X_{22}a_1b_2 & X_{22}a_1b_3\\ X_{21}a_2b_1 & X_{21}a_2b_2 & X_{21}a_2b_3 & X_{22}a_2b_1 & X_{22}a_2b_2-\omega & X_{22}a_2b_3\\ X_{21}a_3b_1 & X_{21}a_3b_2 & X_{21}a_3b_3 & X_{22}a_3b_1 & X_{22}a_3b_2 & X_{22}a_3b_3-\omega \end{vmatrix}.$$

We make the column transformations

$$C_2'=C_2-C_1\frac{b_2}{b_1},\quad C_3'=C_3-C_1\frac{b_3}{b_1},\quad C_5'=C_5-C_4\frac{b_2}{b_1},\quad C_6'=C_6-C_4\frac{b_3}{b_1}$$

$$0=\det\begin{vmatrix} X_{11}a_1b_1-\omega & \omega\frac{b_2}{b_1} & \omega\frac{b_3}{b_1} & X_{12}a_1b_1 & 0 & 0\\ X_{11}a_2b_1 & -\omega & 0 & X_{12}a_2b_1 & 0 & 0\\ X_{11}a_3b_1 & 0 & -\omega & X_{12}a_3b_1 & 0 & 0\\ X_{21}a_1b_1 & 0 & 0 & X_{22}a_1b_1-\omega & \omega\frac{b_2}{b_1} & \omega\frac{b_3}{b_1}\\ X_{21}a_2b_1 & 0 & 0 & X_{22}a_2b_1 & -\omega & 0\\ X_{21}a_3b_1 & 0 & 0 & X_{22}a_3b_1 & 0 & -\omega \end{vmatrix}.$$

Then we make the row transformations

$$R_1^{'} = R_1 + R_2\frac{b_2}{b_1} + R_3\frac{b_3}{b_1}, \quad R_4^{'} = R_4 + R_5\frac{b_2}{b_1} + R_6\frac{b_3}{b_1},$$

$$0 = \det \begin{vmatrix} X_{11}(a_1b_1 + a_2b_2 + a_3b_3) - \omega & 0 & 0 & X_{12}(a_1b_1 + a_2b_2 + a_3b_3) & 0 & 0 \\ X_{11}a_2b_1 & -\omega & 0 & X_{12}a_2b_1 & 0 & 0 \\ X_{11}a_3b_1 & 0 & -\omega & X_{12}a_3b_1 & 0 & 0 \\ X_{21}(a_1b_1 + a_2b_2 + a_3b_3) & 0 & 0 & X_{22}(a_1b_1 + a_2b_2 + a_3b_3) - \omega & 0 & 0 \\ X_{21}a_2b_1 & 0 & 0 & X_{22}a_2b_1 & -\omega & 0 \\ X_{21}a_3b_1 & 0 & 0 & X_{22}a_3b_1 & 0 & -\omega \end{vmatrix},$$

i.e. $\omega = 0$ (four times) or

$$0 = \det \begin{vmatrix} X_{11}(a_1b_1 + a_2b_2 + a_3b_3) - \omega & X_{12}(a_1b_1 + a_2b_2 + a_3b_3) \\ X_{21}(a_1b_1 + a_2b_2 + a_3b_3) & X_{22}(a_1b_1 + a_2b_2 + a_3b_3) - \omega \end{vmatrix},$$

i.e. the eigenvalues are $(a_1b_1+a_2b_2+a_3b_3)$ multiplied by the eigenvalues of the matrix

$$\begin{vmatrix} X_{11} & X_{12} \\ X_{21} & X_{22} \end{vmatrix}.$$

In other words the spectral radius of the matrix $\mathbf{M}$ is $\xi\rho(\mathbf{X})$.

In the case of q shooting galleries the proof is similar, just perform the column operations:

$$C_2^{'} = C_2 - C_1\frac{b_2}{b_1}, \quad C_3^{'} = C_3 - C_1\frac{b_3}{b_1}, \quad C_5^{'} = C_5 - C_4\frac{b_2}{b_1}, \quad C_6^{'} = C_6 - C_4\frac{b_3}{b_1}$$
$$\ldots, C_{3q-1}^{'} = C_{3q-1} - C_{3q-2}\frac{b_2}{b_1}, C_{3q}^{'} = C_{3q} - C_{3q-2}\frac{b_3}{b_1}.$$

Then perform the row operations:

$$R_1^{'} = R_1 + R_2\frac{b_2}{b_1} + R_3\frac{b_3}{b_1}, \quad R_4^{'} = R_4 + R_5\frac{b_2}{b_1} + R_6\frac{b_3}{b_1}$$

$$\ldots R_{3q-2}^{'} = R_{3q-2} + R_{3q-1}\frac{b_2}{b_1} + R_{3q}\frac{b_3}{b_1}.$$

Hence the spectral radius is $\xi\rho(\mathbf{X})$ or equivalently the spectral radius of the matrix $\hat{\mathbf{Q}}$ where $\hat{\mathbf{Q}} = \xi\mathbf{X}$. Thus from our previous work by (2.16) the expected number of secondary addicts in group k left infected by a single newly infected addict entering group i is

$$Q_{ik} = \xi\sum_{j=1}^{q}\frac{\lambda_i P_{ij}\Lambda_{kj}(1-\phi_{kj})}{\sum_{e=1}^{p}\Lambda_{ej}+\tau_j}, \tag{2.17}$$

where $\xi = (\alpha_y\sigma(1-\delta)+\alpha_h\mu)/\mu(\mu+\sigma)$. We expect the basic reproductive number R_0 to be the largest eigenvalue of the $p\times p$ matrix $\mathbf{Q}$, with $Q_{ik}\geq 0$ for $i,k = 1,2,\ldots,p$. Recall that $\rho(\mathbf{Q})$ the spectral radius of $\mathbf{Q}$, is defined to be the modulus of the largest eigenvalue of $\mathbf{Q}$ or:

$$\rho(\mathbf{Q}) = \max_{1\leqslant i\leqslant p} \mid \lambda_i \mid \tag{2.18}$$

where $\lambda_1, \lambda_2, \ldots \lambda_p$ are the eigenvalues of $\mathbf{Q}$. Note that the matrices $\mathbf{Q}$ and $\hat{\mathbf{Q}}$ defined by:

$$Q_{ik} = \xi\sum_{j=1}^{q}\frac{\lambda_i P_{ij}\Lambda_{kj}(1-\phi_{kj})}{\sum_{e=1}^{p}\Lambda_{ej}+\tau_j}, \tag{2.19}$$

and

$$\hat{Q}_{jr} = \xi\sum_{k=1}^{p}\frac{\Lambda_{kj}(1-\phi_{kj})\lambda_k P_{kr}}{\sum_{e=1}^{p}\Lambda_{ej}+\tau_j}, \tag{2.20}$$

have the same spectral radius. The following lemma is quoted from Lemma 3.3 of Greenhalgh (1996) which says:

Lemma 2.3.1. *If $\boldsymbol{A}$ is a $p \times q$ matrix and $\boldsymbol{B}$ is $q \times p$ matrix then $\rho(\boldsymbol{AB}) = \rho(\boldsymbol{BA})$.*

Proof. Proved in Greenhalgh (1996). □

Lemma 2.3.2. *Let $\boldsymbol{Q}$ and $\hat{\mathbf{Q}}$ be as defined above, then $\rho(\boldsymbol{Q}) = \rho(\hat{\mathbf{Q}})$.*

Proof. To prove this Lemma we write $\mathbf{P} = [\xi\lambda_i P_{ij}]_{p\times m}$ and

$$\mathbf{R} = \left[\frac{\Lambda_{ij}(1-\phi_{ij})}{\sum_{e=1}^{p}\Lambda_{ej}+\tau_j}\right]_{p\times m},$$

then $\mathbf{Q} = \mathbf{AB}$ (i.e. $Q_{ik} = \sum_{j=1}^{q} A_{ij}B_{jk}$) where $\mathbf{A} = \mathbf{P}$ and $\mathbf{B} = \mathbf{R}^T$

$$\hat{\mathbf{Q}} = \mathbf{BA} = \sum_{k=1}^{p} B_{jk}A_{kr}.$$

Then $\rho(\mathbf{AB}) = \rho(\mathbf{BA})$ by Lemma 2.3.1. □

R_0 is of critical importance in epidemiological models with the disease usually dying out when $R_0 \leq 1$ and an epidemic usually occurring when $R_0 > 1$. In the above section we described a completely general model for addicts visiting shooting galleries where addicts had a completely general choice of shooting galleries to visit. We now look at some special situations of this where the expression obtained for the basic reproductive number simplifies. In particular, we are interested in the cases that allow R_0 to be as small a value as possible.

2.4 Minimisation of R_0

The magnitude of R_0 allows us to determine the amount of control effort which is sufficient to control the spread of disease. By determining parameter values that

minimise R_0 we can determine whether a given control strategy will eliminate disease or not. In this section we shall look at the following cases:

1. The effect of addicts in different groups visiting shooting galleries at different rates on R_0.

2. Optimal allocation of limited needle exchange effort between different shooting galleries.

3. Optimal allocation of limited needle cleaning effort between different groups of addicts and shooting galleries.

2.4.1 Optimal Scenario of Addicts in Different Groups Visiting Shooting Galleries at Different Rates

We shall start off by looking at the effect on R_0 of addicts in different groups visiting shooting galleries at different rates. In the first instance we shall look at the situation where addicts of type i, for $i = 1, 2, \ldots p$ choose the needles at random. As there are m_j needles in shooting gallery j and m needles altogether, this implies that $P_{ij} = m_j/m$. Hence, equation (2.20) becomes:

$$\begin{aligned} \hat{Q}_{jr} &= \frac{\xi \sum_{k=1}^{p} \lambda_k \frac{m_r}{m} \lambda_k \frac{m_j}{m} \frac{n_k}{m_j} (1 - \phi_{kj})}{\sum_{l=1}^{p} \lambda_l \frac{n_l}{m_j} \frac{m_j}{m} + \tau_j}, \\ &= \frac{\xi \sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m^2} (1 - \phi_{kj}) m_r}{\sum_{l=1}^{p} \lambda_l \frac{n_l}{m} + \tau_j}. \end{aligned}$$

Note that the matrix Q_{jr} has the form $a_j b_r$ where:

$$a_j = \frac{\xi \sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m^2} (1 - \phi_{kj})}{\sum_{l=1}^{p} \lambda_l \frac{n_l}{m} + \tau_j} \quad \text{and} \quad b_r = m_r.$$

Lemma 2.4.1. *If* $\boldsymbol{Q} = [a_j b_k]_{q\times q}$ *is a matrix with* $Q_{jk} = a_j b_k$, *for* $j, k = 1, 2, \ldots, q$, *then* $\rho(\boldsymbol{Q}) = \sum_{j=1}^{q} a_j b_j$.

Proof. The characteristic equation of $\mathbf{Q}$ is:

$$0 = \det(\mathbf{Q} - \omega\mathbf{I}),$$

$$= \det \begin{vmatrix} a_1b_1 - \omega & a_1b_2 & a_1b_3 & \ldots & a_1b_q \\ a_2b_1 & a_2b_2 - \omega & a_2b_3 & \ldots & a_2b_q \\ \vdots & \vdots & \vdots & & \vdots \\ a_qb_1 & a_qb_2 & a_qb_3 & \ldots & a_qb_q - \omega \end{vmatrix}.$$

Subtracting row q multiplied by a_i/a_q from the ith row for $i = 1, 2, \ldots, q-1$ will not change the determinant so this characteristic equation is:

$$0 = \det \begin{vmatrix} -\omega & 0 & 0 & 0 & \ldots & \omega\frac{a_1}{a_q} \\ 0 & -\omega & 0 & 0 & \ldots & \omega\frac{a_2}{a_q} \\ 0 & 0 & -\omega & 0 & \ldots & \omega\frac{a_3}{a_q} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ a_qb_1 & a_qb_2 & a_qb_3 & & \ldots & a_qb_q - \omega \end{vmatrix}.$$

Expanding the determinant along the last column we see that it is:

$$-\omega\frac{a_1}{a_q}a_qb_1(-\omega)^{q-2} + (-\omega)\frac{a_2}{a_q}a_qb_2(-\omega)^{q-2} + \cdots +$$

$$(-\omega)\frac{a_{q-1}}{a_q}a_qb_{q-1}(-\omega)^{q-2} + (-\omega)^{q-1}a_qb_q + (-\omega)^q = 0.$$

Dividing by $(-1)^{q-1}$ we have

$$\omega^q - \omega^{q-1}(a_1b_1 + a_2b_2 + \cdots + a_qb_q) = 0.$$

Hence the eigenvalues are $\omega = 0$ $(q-1)$ times and

$$\omega = a_1b_1 + a_2b_2 + \cdots + a_qb_q,$$

and the spectral radius is the largest eigenvalue which is

$$\sum_{j=1}^{q} a_jb_j.$$

□

As a result, we deduce that:

$$\rho(\hat{\mathbf{Q}}) = \sum_{j=1}^{q} Q_{jj},$$

$$= \frac{\xi \sum_{j=1}^{q} m_j \sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m^2}(1-\phi_{kj})}{\sum_{l=1}^{p} \lambda_l \frac{n_l}{m} + \tau_j}. \tag{2.21}$$

To simply the expression of $\rho(\hat{\mathbf{Q}})$, let us assume that the needle cleaning rate depends only on j, so that $\phi_{ij} = \phi_j$ for $i = 1, 2, \ldots, p$ and $j = 1, 2, \ldots, q$. Moreover, we also assume that the population is homogeneous in needle exchange rate, which implies that $\tau_j = \tau$ for $j = 1, 2, \ldots, q$,

$$\rho(\hat{\mathbf{Q}}) = \frac{\sum_{k=1}^{p} \lambda_k^2 n_k}{\sum_{l=1}^{p} \frac{\lambda_l n_l}{m} + \tau} \; \frac{\xi}{m^2} \sum_{j=1}^{q} m_j(1-\phi_j). \tag{2.22}$$

Note that the *Cauchy-Schwarz* inequality (Steele, 2004) states that for any pairs of sets of real numbers $x_1, x_2, \ldots, x_p, y_1, y_2, \ldots, y_p$

$$\Big(\sum_{i=1}^{p} x_i y_i\Big)^2 \;\leq\; (\sum_{i=1}^{p} x_i)^2 (\sum_{i=1}^{p} y_i)^2.$$

Here, let us choose $x_i = \sqrt{n}_i$, $y_i = \sqrt{n}_i \lambda_i$ for $i = 1, 2, \ldots p$. We deduce that:

$$\Big(\sum_{i=1}^{p} n_i \lambda_i\Big)^2 \;\leq\; (\sum_{i=1}^{p} n_i)(\sum_{i=1}^{p} n_i \lambda_i^2).$$

Hence

$$\Big(\sum_{i=1}^{p} n_i \lambda_i^2\Big) \;\geq\; \frac{(\sum_{i=1}^{p} n_i \lambda_i)^2}{\sum_{i=1}^{p} n_i}.$$

So

$$\rho(\hat{\mathbf{Q}}) \;\geq\; \frac{(\sum_{i=1}^{p} n_i \lambda_i)^2 / \sum_{i=1}^{p} n_i}{\sum_{i=1}^{p} \frac{\lambda_i n_i}{m} + \tau} \; \frac{\xi}{m^2} \sum_{j=1}^{q} m_j (1 - \phi_j).$$

Therefore,

$$\rho(\hat{\mathbf{Q}}) \;\geq\; \frac{n\overline{\lambda}^{\,2}}{\frac{n\overline{\lambda}}{m} + \tau} \; \frac{\xi}{m^2} \sum_{j=1}^{q} m_j (1 - \phi_j).$$

Here

$$\overline{\lambda} = \frac{\sum_{i=1}^{p} n_i \lambda_i}{\sum_{i=1}^{p} n_i},$$

is the average sharing rate of drug injectors in shooting galleries. However, this is the value of R_0 when $\lambda_1 = \lambda_2 = \cdots = \lambda_p = \overline{\lambda}$. So in this situation where the addicts choose needles at random, $P_{ij} = m_j/m$, the needle cleaning rate depends only on the shooting gallery, so that $\phi_{ij} = \phi_j$, all addicts visiting shooting galleries at the same

ratr, minimises R_0.

Now, we assume that $P_{ij} = P_j$ but that this value is not necessarily equal to m_j/m (the probabilities P_{ij} can take any positive values but these values must sum to one). We again assume that the needle cleaning probability $\phi_{ij} = \phi_j$ depends on the shooting gallery j but not the addict group i. The needle exchange rate τ_j depends only on the shooting gallery. Thus, we have that:

$$\hat{Q}_{jr} = \frac{\xi \sum_{k=1}^{p} \lambda_k P_r \Lambda_{kj}(1-\phi_j)}{\sum_{l=1}^{p} \lambda_l \frac{n_l}{m_j} P_j + \tau_j}.$$

Again $\hat{Q}_{jr}$ factorises as $a_j b_r$ where:

$$a_j = \frac{\xi \sum_{k=1}^{p} \lambda_k \Lambda_{kj}(1-\phi_j)}{\sum_{l=1}^{p} \lambda_l \frac{n_l}{m_j} P_j + \tau_j} \qquad \text{and} \qquad b_r = P_r,$$

so $\rho(\hat{\mathbf{Q}}) = \sum_{j=1}^{q} \hat{Q}_{jj}$,

$$\rho(\hat{\mathbf{Q}}) = \frac{\sum_{j=1}^{q} \xi \sum_{k=1}^{p} \lambda_k^2 P_j^2 \frac{n_k}{m_j}(1-\phi_j)}{\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j} + \tau_j}. \tag{2.23}$$

This is the expression of R_0 in (2.17). Now, we will show that again all addicts equally likely to visit all shooting galleries (i.e. $\lambda_1 = \lambda_2 = \cdots = \lambda_p = \overline{\lambda}$) minimises R_0. We rewrite the equation (2.23) as the following:

$$\rho(\hat{\mathbf{Q}}) = \sum_{j=1}^{q} \frac{\xi \sum_{k=1}^{p} \lambda_k^2 n_k \frac{P_j^2}{m_j}(1-\phi_j)}{\sum_{l=1}^{p} \lambda_l n_l \frac{P_j}{m_j} + \tau_j}.$$

As before, we deduce that:

$$\sum_{i=1}^{p} n_i \lambda_i^2 \geq \frac{(\sum_{i=1}^{p} n_i \lambda_i)^2}{\sum_{i=1}^{p} n_i}.$$

So,

$$\rho(\hat{\mathbf{Q}}) \geq \frac{\left(\sum_{i=1}^{p} n_i \lambda_i\right)^2}{\sum_{i=1}^{p} n_i} \sum_{j=1}^{q} \frac{\xi \frac{P_j^2}{m_j}(1-\phi_j)}{\sum_{l=1}^{p} \lambda_l n_l \frac{P_j}{m_j} + \tau_j}. \tag{2.24}$$

The right-hand side of (2.24) is the value of R_0 when all addicts visit all shooting galleries at the same rate, so this minimises the value of R_0.

2.4.2 Optimal Allocation of Limited Needle Exchange Effort between Different Shooting Galleries

We wish to allocate a given amount of needle exchange effort to have the maximum effect. It seems reasonable to assume that this will have the most effect when R_0 is as small as possible. Hence our problem can be written mathematically as 'choose $\tau_1, \tau_2, \ldots, \tau_q \geq 0$ subject to $\sum_{j=1}^{q} \tau_j \leq \tau$ to minimise R_0'. To do this we use the *Lagrange multiplier* and set up the Lagrangian method. We introduce a new variable ψ, called the Lagrange multiplier, and set up the Lagrange function.

We first deal with the situation where the needle cleaning probability ϕ_{ij} depends only on the shooting gallery j not the addict group i and addicts choose needles at random so that $P_{ij} = m_j/m$. The needle exchange rate τ_j depends on the shooting gallery j. Recall that from equation (2.22) if $\gamma = n/m$ is the gallery ratio of addicts

per needle:

$$R_0 = \xi \sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m} \sum_{j=1}^{q} \frac{\frac{m_j}{m}(1-\phi_j)}{\gamma\bar{\lambda} + \tau_j}.$$

The Lagrange function is:

$$\begin{aligned} F_1 &= \xi \sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m} \sum_{j=1}^{q} \frac{\frac{m_j}{m}(1-\phi_j)}{\overline{\lambda}\gamma + \tau_j} + \psi\left(\tau - \sum_{j=1}^{q} \tau_j\right), \\ &= \frac{\xi}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k \sum_{j=1}^{q} \frac{m_j(1-\phi_j)}{\overline{\lambda}\gamma + \tau_j} + \psi\left(\tau - \sum_{j=1}^{q} \tau_j\right). \end{aligned} \tag{2.25}$$

The necessary conditions for a local minimum requires the first-order conditions equal to zero:

$$\frac{\partial F_1}{\partial \tau_j} = \frac{-\xi}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k \frac{m_j(1-\phi_j)}{(\overline{\lambda}\gamma + \tau_j)^2} - \psi = 0 \tag{2.26}$$

as the equation (2.26) gives the optimum values of τ_j when $\partial F_1/\partial \tau_j = 0$, we have at $\tau_j = \hat{\tau}_j$:

$$\psi = \frac{-\xi}{m^2} \sum_{k=1}^{p} \frac{\lambda_k^2 n_k m_j (1-\phi_j)}{(\overline{\lambda}\gamma + \hat{\tau}_j)^2} \ .$$

Hence

$$\overline{\lambda}\gamma + \hat{\tau}_j = \sqrt{\frac{-\xi \sum_{l=1}^{p} \lambda_l^2 n_l m_j (1-\phi_j)}{m^2 \psi}} \ ,$$

so,

$$\hat{\tau}_j = \sqrt{\frac{-\xi \sum_{k=1}^{p} \lambda_k^2 n_k m_j (1-\phi_j)}{m^2 \psi}} - \overline{\lambda}\gamma. \tag{2.27}$$

To find the optimal value of τ_j we rearrange the above equation and choose $\psi < 0$. So that $\sum_{j=1}^{q} \hat{\tau}_j = \tau$:

$$\begin{aligned}
\tau &= \frac{1}{\sqrt{-\psi}} \sum_{j=1}^{q} \sqrt{\frac{\xi \sum_{k=1}^{p} \lambda_k^2 n_k m_j (1-\phi_j)}{m^2}} - q\overline{\lambda}\gamma, \\
\tau + q\overline{\lambda}\gamma &= \frac{1}{\sqrt{-\psi}} \sum_{j=1}^{q} \sqrt{\frac{\xi \sum_{k=1}^{p} \lambda_k^2 n_k m_j (1-\phi_j)}{m^2}}, \\
\sqrt{-\psi} &= \frac{1}{\tau + q\overline{\lambda}\gamma} \sum_{j=1}^{q} \sqrt{\frac{\xi \sum_{k=1}^{p} \lambda_k^2 n_k m_j (1-\phi_j)}{m^2}}, \\
\psi &= \frac{-1}{(\tau + q\overline{\lambda}\gamma)^2} \left[\sum_{j=1}^{q} \sqrt{\frac{\xi \sum_{k=1}^{p} \lambda_k^2 n_k m_j (1-\phi_j)}{m^2}} \right]^2. \quad (2.28)
\end{aligned}$$

To check that it is a minimum value which minimises R_0, we take the second-order partial derivative of F_1:

$$\frac{\partial^2 F_1}{\partial \tau_i \partial \tau_j} = \begin{cases} 0, & \text{if } i \neq j; \\ \frac{2\xi}{m^2} \frac{\sum_{k=1}^{p} \lambda_k^2 n_k m_j (1-\phi_j)}{(\overline{\lambda}\gamma + \tau_j)^3} > 0, & \text{if } i = j. \end{cases}$$

Hence we notice that $\hat{\tau}_j$ is a minimum as $\partial^2 F_1 / \partial \tau_i \partial \tau_j$ is a positive definite matrix. The minimised value of R_0 is:

$$F_1 = \frac{\xi}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k \sum_{j=1}^{q} \frac{m_j (1-\phi_j)}{\overline{\lambda}\gamma + \hat{\tau}_j},$$

but substituting the value of ψ from the equation (2.28) into the equation (2.27) we deduce that:

$$\overline{\lambda}\gamma + \hat{\tau}_j = \frac{\sqrt{\xi \sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m} \frac{m_j}{m} (1-\phi_j)} \;\; (\tau + q\overline{\lambda}\gamma)}{\sum_{j=1}^{q} \sqrt{\xi \sum_{i=1}^{p} \lambda_i^2 \frac{n_i}{m} \frac{m_j}{m} (1-\phi_j)}},$$

so

$$F_1 = \frac{\xi}{(\tau + q\overline{\lambda}\gamma)} \sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m} \left[\sum_{j=1}^{q} \sqrt{\frac{m_j}{m}(1-\phi_j)} \right]^2, \tag{2.29}$$

is actually the minimum value.

Now we look at the case where all the $\tau' s$ are equal, so $\tau_1 = \tau_2 = \cdots = \tau_q = \tau/q$. In this case:

$$\begin{aligned} R_0 = R_0^E &= \sum_{k=1}^{p} \frac{n_k \lambda_k^2}{m} \frac{\xi \sum_{j=1}^{q} \frac{m_j}{m}(1-\phi_j)}{\overline{\lambda}\gamma + \tau/q}, \\ &= \sum_{k=1}^{p} \frac{n_k \lambda_k^2}{m} \frac{q\xi}{q\overline{\lambda}\gamma + \tau} \sum_{j=1}^{q} \frac{m_j}{m}(1-\phi_j). \end{aligned}$$

We shall now verify that this value of R_0^E exceeds the minimum value that we have just found (2.29) as:

$$q \sum_{j=1}^{q} \frac{m_j}{m}(1-\phi_j) \geq \left[\sum_{j=1}^{q} \sqrt{\frac{m_j}{m}(1-\phi_j)} \right]^2.$$

Indeed for any set of positive numbers $a_1, a_2, \ldots, a_q$ let $\mathbf{a}$ and $\mathbf{1}$ be two vectors of positive numbers where:

$$\mathbf{a} = (a_1, a_2, \ldots, a_q),$$

and

$$\mathbf{1} = (1, 1, \ldots, 1), \qquad q \text{ times.}$$

Using the *dot* product to multiply these vectors, gives us the following:

$$| \mathbf{a} \cdot \mathbf{1} | = \| \mathbf{a} \| \cdot \| \mathbf{1} \| \cos\theta, \tag{2.30}$$

where $\| \mathbf{a} \|$ and $\| \mathbf{1} \|$ are the length of the two vectors and θ is the angle between them. Note that:

$$\begin{aligned} \| \mathbf{a} \| &= \sqrt{a_1^2 + a_2^2 + \cdots + a_q^2}, \\ | \mathbf{a} \cdot \mathbf{1} |^2 &\leq \| \mathbf{a} \|^2 \cdot \| \mathbf{1} \|^2 . \end{aligned}$$

Hence (2.30) yields:

$$| \sum_{j=1}^{q} a_j |^2 \leq q \, | \sum_{j=1}^{q} a_j^2 | .$$

This also follows from the Cauchy-Schwarz inequality discussed earlier. We take $a_j = \sqrt{\frac{m_j}{m}(1-\phi_j)}$, so:

$$\left[\sum_{j=1}^{q} \sqrt{\frac{m_j}{m}(1-\phi_j)} \right]^2 \leq q \sum_{j=1}^{q} \frac{m_j}{m}(1-\phi_j),$$

then we get the required result that R_0^E exceeds the minimum value of R_0 given by the equation (2.29).

The second case that we shall discuss is when the probability P_{ij} giving the choice of shooting galleries is given by $P_{ij} = m_j/m$ but the needle cleaning probability ϕ_{ij} depends on both the addict group i and the shooting gallery j. Recall equation (2.21):

$$\rho(\hat{\mathbf{Q}}) = \xi \sum_{j=1}^{q} m_j \frac{\sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m^2}(1-\phi_{kj})}{\tau_j + \sum_{l=1}^{p} \frac{\lambda_l n_l}{m}}.$$

Again, we use the Lagrange multiplier technique to minimise $\rho(\hat{\mathbf{Q}})$ subject to $\sum_{j=1}^{q} \tau_j = \tau$. The objective function is:

$$F_2 = \xi \sum_{j=1}^{q} m_j \frac{\sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m^2}(1-\phi_{kj})}{\tau_j + \sum_{l=1}^{p} \frac{\lambda_l n_l}{m}}. \tag{2.31}$$

As we did previously, we use the Lagrange method to minimise $\rho(\hat{\mathbf{Q}})$. The Lagrange function is:

$$F_2 = \xi \sum_{j=1}^{q} m_j \frac{\sum_{k=1}^{p} \lambda_k^2 \frac{n_k}{m^2}(1-\phi_{kj})}{\tau_j + \sum_{l=1}^{p} \frac{\lambda_l n_l}{m}} + \psi\left(\tau - \sum_{j=1}^{q} \tau_j\right).$$

Necessary conditions for a minimum require setting all first order derivatives to zero. This occurs when $\tau_j = \hat{\tau}_j$ for $j = 1, 2, \ldots, q$.

$$\frac{\partial F_2}{\partial \tau_j} = \frac{-\xi \frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})}{(\overline{\lambda}\gamma + \tau_j)^2} - \psi = 0.$$

Hence

$$\begin{aligned}
\psi &= \frac{-\xi \frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})}{(\overline{\lambda}\gamma + \tau_j)^2}, \\
\overline{\lambda}\gamma + \hat{\tau}_j &= \sqrt{\frac{-\xi \frac{m_j}{m} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})}{\psi}}, \\
\hat{\tau}_j &= \sqrt{\frac{-\xi \frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})}{\psi}} - \overline{\lambda}\gamma.
\end{aligned}$$

To find the optimal value of $\hat{\tau}_j$, choose $\psi < 0$, to satisfy $\sum_{j=1}^{q} \hat{\tau}_j = \tau$.

$$\begin{aligned}
\sum_{j=1}^{q} \hat{\tau}_j &= \sum_{j=1}^{q} \sqrt{\frac{-\xi \frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})}{\psi}} - q\overline{\lambda}\gamma, \\
\tau &= (-\psi)^{-1/2} \sum_{j=1}^{q} \sqrt{\xi \frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})} - q\overline{\lambda}\gamma, \\
\tau + q\overline{\lambda}\gamma &= (-\psi)^{-1/2} \sum_{j=1}^{q} \sqrt{\xi \frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})}.
\end{aligned}$$

To check that the solution is indeed a minimum value which minimises R_0, we take the second-order derivative of (2.31). We deduce that at $\tau_j = \hat{\tau}_j$:

$$\frac{\partial^2 F_2}{\partial \tau_i \partial \tau_j} = \begin{cases} 0, & \text{if } i \neq j, \\ \frac{2\xi \frac{m_j}{m} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})\xi}{(\overline{\lambda}\gamma + \hat{\tau}_j)^3} > 0, & \text{if } i = j. \end{cases}$$

The minimised value of F_2 is:

$$(-\psi)^{1/2} \sum_{j=1}^{q} \sqrt{\xi \frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})}$$

$$= \frac{\xi}{(\tau + q\overline{\lambda}\gamma)} \left[\sum_{j=1}^{q} \sqrt{\frac{m_j}{m^2} \sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi_{kj})} \right]^2.$$

In the case where $\phi_{kj} = \phi_j$ is independent of the group of addict this reduces to what we had previously in (2.29).

The next case that we want to survey is how to choose the needle exchange effort within a constraint to minimise R_0 when P_{ij}, the probability that an addict of type i chooses a needle in shooting gallery j depends on the shooting gallery j and not the addict group i, but P_j is not necessarily equal to m_j/m. The equation (2.20) becomes:

$$\hat{Q}_{jr} = \xi \frac{\sum_{k=1}^{p} \lambda_k P_r \Lambda_{kj} (1-\phi_{kj})}{\sum_{l=1}^{p} \Lambda_{lj} + \tau_j},$$

$$= \xi \frac{\sum_{k=1}^{p} \lambda_k^2 P_j P_r \frac{n_k}{m_j} (1-\phi_{kj})}{\sum_{l=1}^{p} \lambda_l P_j \frac{n_l}{m_j} + \tau_j}.$$

Note that we found earlier that $\rho(\hat{\mathbf{Q}}) = \sum_{j=1}^{q} \hat{Q}_{jj}$, so:

$$\rho(\hat{\mathbf{Q}}) = \sum_{j=1}^{q} \xi \frac{\sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j} + \tau_j}.$$

Then we are performing a similar process by using the Lagrangian method to find the optimal allocation of τ_j subject to the constraint $\sum_{j=1}^{q} \tau_j = \tau$, and $\rho(\hat{\mathbf{Q}})$ is the objective function. The Lagrangian is:

$$F_3 = \xi \sum_{j=1}^{q} \frac{\sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j} + \tau_j} + \psi \left(\tau - \sum_{j=1}^{q} \tau_j \right).$$

The necessary conditions for a local minimum requires the following:

$$\frac{\partial F_3}{\partial \tau_j} = \frac{-\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\left(\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j} + \tau_j \right)^2} - \psi = 0.$$

This implies that:

$$\psi = \frac{-\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\left(\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j} + \hat{\tau}_j \right)^2}.$$

Thus:

$$\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j} + \hat{\tau}_j = \sqrt{\frac{-\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\psi}},$$

$$\hat{\tau}_j = \sqrt{\frac{-\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\psi}} - \sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j}.$$

To find the optimal value of τ_j, we choose $\psi < 0$ such that:

$$\begin{aligned}
\tau = \sum_{j=1}^{q} \tau_j &= \sum_{j=1}^{q} \sqrt{\frac{-\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\psi}} - \sum_{j=1}^{q}\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j}, \\
\tau + \sum_{l=1}^{p} n_l \lambda_l \sum_{j=1}^{q} \frac{P_j}{m_j} &= (-\psi)^{-1/2} \sum_{j=1}^{q} \sqrt{\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}.
\end{aligned}$$

This implies that:

$$\psi = \frac{-\left[\sum_{j=1}^{q} \sqrt{\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}\ \right]^2}{\left(\tau + \sum_{l=1}^{p} n_l \lambda_l \sum_{j=1}^{q} \frac{P_j}{m_j}\right)^2}.$$

Hence, the minimised value of F_3 is:

$$\sum_{j=1}^{q} \frac{\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\sum_{l=1}^{p} n_l \lambda_l \frac{P_j}{m_j} + \hat{\tau}_j} = \sum_{j=1}^{q} \frac{\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}{\sqrt{\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}}\ \sqrt{-\psi},$$

$$= \frac{\left[\sum_{j=1}^{q} \sqrt{\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{kj})}\ \right]^2}{\tau + \sum_{l=1}^{p} n_l \lambda_l \sum_{j=1}^{q} \frac{P_j}{m_j}}.$$

In the special case where the needle cleaning probability ϕ_{ij} depends only on the shooting gallery j not the addict group i, we substitute ϕ_j for ϕ_{ij} in the value of F_3 to obtain:

$$= \frac{\left[\sum_{j=1}^{q} \sqrt{\xi \sum_{k=1}^{p} n_k \lambda_k^2 \frac{P_j^2}{m_j}(1-\phi_{j})}\ \right]^2}{\tau + \sum_{l=1}^{p} n_l \lambda_l \sum_{j=1}^{q} \frac{P_j}{m_j}},$$

as the minimum value of R_0.

2.4.3 Optimal Allocation of Limited Needle Cleaning Effort between Different Groups of Addicts and Shooting Galleries

We have considered the problem of how to allocate limited resources of needle exchange effort between shooting galleries used by competing groups of addicts. However, needle exchange is only one way to reduce HCV prevalence. Another way is to allocate needle cleaning materials such as bleach between the different shooting galleries, or alternatively educate the addicts to use efficient needle cleaning practices. Now we shall discuss the needle cleaning probability choice that minimises the value of R_0. Again there is a given total amount of resource available to use, so that:

$$\sum_{i=1}^{p}\sum_{j=1}^{q}\phi_{ij} \leq \Phi.$$

We return to the case where addicts choose needles at random, so $P_{ij} = m_j/m$, and needle exchange is heterogeneous so there is an amount τ_j of effort applied in shooting gallery j. Then:

$$\begin{aligned} R_0 &= \sum_{j=1}^{q} m_j \frac{\sum_{k=1}^{p} \frac{n_k\lambda_k^2}{m^2}(1-\phi_{kj})\xi}{\sum_{l=1}^{p}\frac{n_l\lambda_l}{m}+\tau_j}, \\ &= \sum_{j=1}^{q}\sum_{k=1}^{p} a_k b_j (1-\phi_{kj})\xi, \end{aligned}$$

where $a_k = n_k\lambda_k^2/m^2$ and $b_j = m_j/(\sum_{l=1}^{p}\frac{n_l\lambda_l}{m}+\tau_j)$. The mathematical problem is then to choose ϕ_{kj} subject to $0 \leq \phi_{kj} \leq 1$ and $\sum_{k=1}^{p}\sum_{j=1}^{q}\phi_{kj} \leq \Phi$ to minimise R_0. Clearly the value of ϕ_{kj} that produces the maximal reduction in R_0 is the value

(k_0, j_0) of (k, j) that maximises $a_k b_j$. Hence, we should apply the maximum amount of that possible.

If $\Phi < 1$ then we should choose $\phi_{k_0,j_0} = \Phi$ and we are finished. If $\Phi \geq 1$ then we should choose $\phi_{k_0,j_0} = 1$ and look for the pair (k, j) that maximises $a_k b_j$ over the remaining values of k and j say (k_1, j_1) and apply the maximum amount of control effort possible to that, and so on, until either we have used up all of the needle cleaning effort Φ possible or $R_0 = 0$. Hence, in this case the optimal policy is to successively apply the maximal amount of needle cleaning effort possible to the group k and shooting gallery j that has the maximum value of $a_k b_j$ until the needle cleaning effort available is exhausted.

Similarly we can consider the problem of minimising R_0 subject to $\sum_{k=1}^{p} \sum_{j=1}^{q} \phi_{kj} \leq \Phi$ when $P_{kj} = P_j$, not necessarily equal to m_j/m:

$$R_0 = \sum_{j=1}^{q} \frac{\sum_{k=1}^{p} \lambda_k P_j^2 \frac{n_k}{m_j}(1 - \phi_{kj})\xi}{\sum_{l=1}^{p} \lambda_l P_j \frac{n_l}{m_j} + \tau_j},$$

$$= \sum_{j=1}^{q} \sum_{k=1}^{p} c_k d_j (1 - \phi_{kj})\xi,$$

where $c_k = \lambda_k^2 n_k$ and $d_j = P_j^2/(\sum_{l=1}^{p} n_l \lambda_l P_j + m_j \tau_j)$.

Following the same argument as above we deduce that the optimal policy is to successively apply the maximal amount of needle cleaning effort ϕ_{kj} to the pair (k, j) that maximises $c_k d_j$ until we have applied an amount $[\Phi]$ of needle cleaning effort (here $[x]$ denotes the integer part of x) and then we apply the the remaining

amount $\Phi - [\Phi]$ to the pair (k, j) that maximises $c_k d_j$ over the remaining values possible.

2.4.4 Optimal Scenario of Homogeneous Population

Last but not least, we consider the special case where the addict population is homogeneous which means that all addicts visit shooting galleries at the same rate λ. Addicts are assumed to be homogeneous in cleaning rate of needles and random choice of needles, so $\phi_{ij} = \phi$ and $P_{ij} = m_j/m$. We also assume that $\tau_1 = \tau_2 = \cdots = \tau_q = \tau$. From equation (2.20), it is straightforward to show the following:

$$\begin{aligned} \hat{Q}_{jr} &= \frac{\xi \sum_{k=1}^{p} \lambda_k P_{kr} \Lambda_{kj} (1-\phi)}{\sum_{l=1}^{p} \Lambda_{lj} + \tau_j}, \\ &= \frac{\xi \sum_{k=1}^{p} \lambda_k \frac{m_r}{m} \lambda_k \frac{n_k}{m} (1-\phi)}{\sum_{l=1}^{p} \lambda_l \frac{n_l}{m} + \tau_j}. \end{aligned}$$

Now recall that $\sum_{k=1}^{q} m_k = m$, $\lambda_i = \lambda$, $i = 1, 2, \ldots, p$ and $\sum_{i=1}^{p} n_i = n$. Recall also that $R_0 = \rho(\hat{\mathbf{Q}})$ is the spectral radius of $\hat{\mathbf{Q}}$, where the spectral radius is defined to be the largest absolute value of the eigenvalues of the matrix $\hat{\mathbf{Q}}$. $(1, 1, \ldots, 1) \in \mathbb{R}^q$ is a positive right eigenvector of $\hat{\mathbf{Q}}$ with corresponding eigenvalue:

$$\begin{aligned} \lambda(\hat{\mathbf{Q}}) &= \frac{\xi \lambda^2 \gamma (1-\phi)}{\lambda\gamma + \tau}, \\ &= \frac{\xi \lambda (1-\phi)}{1 + \hat{\tau}}, \end{aligned}$$

where $\hat{\tau} = \tau/\lambda\gamma$. By Lemma 2.1 of Nold (1980), we see that:

$$R_0 = \rho(\hat{\mathbf{Q}}) = \max \mid \lambda(\hat{\mathbf{Q}}) \mid .$$

Therefore as the following parameters are defined in Corson et al. model:

$$R_0 = \frac{\lambda(1-\phi)}{\mu(\mu+\sigma)(1+\hat{\tau})}\Big[\mu\alpha_h + \sigma\alpha_y(1-\delta)\Big]. \tag{2.32}$$

This specific case has been considered in the model discussed by Corson et al. (2012) who obtain the same value.

These are the theoretical results concerning the special scenarios that minimise R_0. This completes our discussion of the basic reproductive number. Later on in Chapter Six we shall confirm some of these theoretical results by numerical simulation, and numerically find the impact of different control strategies on the basic reproductive number.

2.5 Conclusion

In this chapter we have developed a mathematical model of the effect of heterogeneity on the prevalence of HCV, building on the models developed by Corson et al. (2012) and Greenhalgh (1996). A system of differential equations has been derived to describe the progress of the disease. Our discussion has ranged from calculating an expression of the important concept of our model, R_0, to finding the special cases and scenarios that minimise this number.

We have shown that if each group of addicts has the same probability of visiting shooting galleries and also the needle cleaning probability depends only on the shooting gallery then all addicts visiting shooting galleries at the same rate min-

imises R_0. We have looked at the problem of allocation of a limited amount of needle exchange effort to have the maximum effect under various conditions. Then we looked at the problem of a allocation of limited amount needle cleaning effect between groups and shooting galleries to minimise R_0. Remember that R_0 is defined as the average number of secondary infections produced by a single infectious individual entering a disease-free population at equilibrium. We expect the disease to take off if $R_0 > 1$ and die out if $R_0 \leq 1$. In the next chapter we shall investigate these conjectures analytically.

Chapter 3

Model Analytical Results

A major project in deterministic modelling of heterogeneous populations is to find conditions for local and global stability of the equilibria and to work out the relations among these stability conditions, the thresholds for disease take off and die out. In this chapter we analyse the behaviour of our transmission model, focusing on the conditions that result in HCV persistence or elimination. We perform an equilibrium and stability analysis in order to determine the nature of any equilibrium solutions. We shall find that the basic reproduction number R_0 is a key parameter in this regard. We shall prove that there are two equilibrium solutions:

- A zero solution (disease-free equilibrium) which is always possible.
- A non-zero solution which is possible if and only if $R_0 > 1$.

We then show that if $R_0 \leq 1$ the disease will always die out, that is the disease-free equilibrium is globally asymptotically stable. Next we show that if $R_0 > 1$ there is a unique non-zero endemic equilibrium solution. For $R_0 > 1$ we shall show that (under mild irreducibility conditions) that the disease-free equilibrium is unstable. Then we show that under the same irreducibility conditions if $R_0 > 1$ and the disease is

initially present then the disease ultimately persists in all groups of addicts and all groups of needles.

3.1 Main Analytical Results

Theorem 3.1.1. *In the system (2.1)-(2.9), if R_0 is less than or equal to unity, the system has a unique equilibrium solution where the disease has died out in each group of addicts and in each shooting gallery.*

Proof. This theorem can be proved in several stages. Let π^*_{xi}, π^*_{si} and β^*_{lj} denote the equilibrium proportions of addicts and needles respectively. The existence of the disease-free equilibrium is obvious with $\pi^*_{xi} = 1$ and $\pi^*_{si} = 0$ where $s = x_1, h_1, h_2, y, z$ and $\beta^*_{lj} = 0$ where $l = h_1, h_2, y$. From the equilibrium versions of equations (2.7) - (2.9), we have the following:

$$\beta^*_{h_1 j} = \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi^*_{h_1 i}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}, \tag{3.1}$$

$$\beta^*_{h_2 j} = \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi^*_{h_2 i}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}, \tag{3.2}$$

and

$$\beta^*_{yj} = \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi^*_{yi}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}. \tag{3.3}$$

From equation (2.3) we have that: $\pi^*_{h_1 i} = (1 - \delta) K_i$ where:

$$K_i = \frac{1}{\mu + \sigma} \sum_{j=1}^{q} (\pi^*_{xi} + \pi^*_{x_1 i}) \lambda_i P_{ij} (1 - \phi_{ij}) (\alpha_h (\beta^*_{h_1 j} + \beta^*_{h_2 j}) + \alpha_y \beta^*_{yj}).$$

Similarly, we have that:

$$\begin{aligned}
\pi^*_{h_2 i} &= \delta K_i, \\
\pi^*_{yi} &= \frac{\sigma(1-\delta)K_i}{\mu}, \\
\pi^*_{zi} &= \frac{\sigma\alpha\delta K_i}{\mu}, \\
\beta^*_{h_1 j} &= \frac{K_i(1-\delta)\sum_{i=1}^{p}\Lambda_{ij}}{\sum_{i=1}^{p}\Lambda_{ij}+\tau_j}, \\
\beta^*_{h_2 j} &= \frac{K_i\delta\sum_{i=1}^{p}\Lambda_{ij}}{\sum_{i=1}^{p}\Lambda_{ij}+\tau_j}, \\
\beta^*_{yj} &= \frac{\sigma(1-\delta)K_i\sum_{i=1}^{p}\Lambda_{ij}}{\mu(\sum_{i=1}^{p}\Lambda_{ij}+\tau_j)}.
\end{aligned} \tag{3.4}$$

We get π^*_{hi} as the following:

$$\begin{aligned}
\pi^*_{hi} &= \pi^*_{h_1 i}+\pi^*_{h_2 i} = (1-\delta)K_i+\delta K_i, \\
&= \frac{1}{\mu+\sigma}\sum_{j=1}^{q}(\pi^*_{xi}+\pi^*_{x_1 i})\lambda_i P_{ij}(1-\phi_{ij})(\alpha_h(\beta^*_{h_1 j}+\beta^*_{h_2 j})+\alpha_y\beta^*_{yj}), \\
&= \frac{1}{\mu+\sigma}\sum_{j=1}^{q}(1-\pi^*_{h_1 i}-\pi^*_{h_2 i}-\pi^*_{yi}-\pi^*_{zi}) \\
&\qquad\qquad \lambda_i P_{ij}(1-\phi_{ij})(\alpha_h(\beta^*_{h_1 j}+\beta^*_{h_2 j})+\alpha_y\beta^*_{yj}), \\
&= \frac{1}{\mu+\sigma}\left(1-\pi^*_{hi}-\frac{\sigma}{\mu}(1-\delta)\pi^*_{hi}-\frac{\sigma}{\mu}\delta\alpha\pi^*_{hi}\right) \\
&\qquad\qquad \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})(\alpha_h(\beta^*_{h_1 j}+\beta^*_{h_2 j})+\alpha_y\beta^*_{yj}), \\
&= \frac{1}{\mu+\sigma}\left(1-\pi^*_{hi}\left(1+\frac{\sigma}{\mu}(1-\delta)+\frac{\sigma}{\mu}\delta\alpha\right)\right) \\
&\qquad\qquad \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\frac{\sum_{k=1}^{p}\Lambda_{kj}\pi^*_{hk}}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\left(\alpha_h+\alpha_y\frac{\sigma}{\mu}(1-\delta)\right), \\
&\leq \sum_{k=1}^{p}Q^*_{ik}\pi^*_{hk}.
\end{aligned} \tag{3.5}$$

Here

$$Q^*_{ik} = \sum_{j=1}^{q} \frac{\xi \lambda_i P_{ij}(1-\phi_{ij})\Lambda_{kj}}{\sum_{k=1}^{p} \Lambda_{kj} + \tau_j}. \tag{3.6}$$

Now, we want to express $\pi^*_{h_1 i}$, $\pi^*_{h_2 i}$, π^*_{yi} and π^*_{zi} in terms of π^*_{hi}. Thus, we have:

$$\begin{aligned}
\pi^*_{h_1 i} &= \frac{(1-\delta)Y_i}{\mu+\sigma}, \\
\pi^*_{h_2 i} &= \frac{\delta Y_i}{\mu+\sigma}, \\
\pi^*_{yi} &= \frac{\sigma(1-\delta)Y_i}{\mu(\mu+\sigma)}, \\
\pi^*_{zi} &= \frac{\sigma\alpha\delta Y_i}{\mu(\mu+\sigma)},
\end{aligned}$$

where:

$$Y_i = \left(1-\pi^*_{hi}\left(1+\frac{\sigma}{\mu}(1-\delta)+\frac{\sigma}{\mu}\delta\alpha\right)\right)\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\frac{\sum_{k=1}^{p}\Lambda_{kj}\pi^*_{hk}}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\left(\alpha_h+\alpha_y\frac{\sigma}{\mu}(1-\delta)\right).$$

Notice that

$$\pi^*_{hi} \leq \sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk},$$

where $\mathbf{Q}^*$ is given by (3.6).

It is clear that the disease-free equilibrium $\pi^*_{xi} = 1$, $\pi^*_{si} = 0$ and $\beta^*_{lj} = 0$ for each i, j is always a solution to the differential equations system (2.1) - (2.9). We need to show that if $R_0 \leq 1$ then there is no other equilibrium solution. To show that we need the following lemma:

Lemma 3.1.2. *The matrix Q^*_{ik} which is defined as follows:*

$$Q^*_{ik} = \sum_{j=1}^{q} \frac{\xi\lambda_i P_{ij}\Lambda_{kj}(1-\phi_{ij})}{\sum_{s=1}^{p}\Lambda_{sj}+\tau_j},$$

has the same eigenvalues as the matrix $\boldsymbol{Q}^T$ where:

$$Q^T_{ik} = Q_{ki} = \sum_{j=1}^{q} \frac{\xi\lambda_k P_{kj}\Lambda_{ij}(1-\phi_{ij})}{\sum_{s=1}^{p}\Lambda_{sj}+\tau_j},$$

see equations (3.6).

Proof. We write

$$a_j = \sum_{s=1}^{p}\Lambda_{sj}+\tau_j.$$

Hence,

$$\begin{aligned} Q^T_{ik} &= \sum_{j=1}^{q} \frac{\xi\lambda_k P_{kj}\Lambda_{ij}(1-\phi_{ij})}{a_j}, \\ &= \sum_{j=1}^{q} \frac{\xi\lambda_k\lambda_i P_{kj}P_{ij}\frac{n_i}{m_j}(1-\phi_{ij})}{a_j}, \\ &= \sum_{j=1}^{q} \frac{\xi\lambda_k\lambda_i P_{kj}P_{ij}\frac{n_k}{m_j}\frac{n_i}{n_k}(1-\phi_{ij})}{a_j}, \\ &= Q^*_{ik}\frac{n_i}{n_k}. \end{aligned}$$

The required result is obtained as it is straightforward to show that if $(e_1,\ e_2,\ldots,\ e_p)$ is a left eigenvector of the matrix Q^T_{ik} then $(n_1e_1,\ n_2e_2,\ldots,\ n_pe_p)$ is a left eigenvector of the matrix Q^*_{ik}. Thus the result follows. □

The following corollary is interesting in view of our previous results.

Corollary 3.1.3. *If the matrix $\hat{Q}^*_{jr}$ is defined as follows:*

$$\hat{Q}^*_{jr} = \frac{\sum_{l=1}^{p} \xi \Lambda_{lr}(1-\phi_{lr})\lambda_l P_{lj}}{\sum_{s=1}^{p} \Lambda_{sr} + \tau_r},$$

then it has the same spectral radius as the matrix Q^T_{ik} where:

$$Q^T_{ik} = Q_{ki} = \sum_{j=1}^{q} \frac{\xi \lambda_k P_{kj} \Lambda_{ij}(1-\phi_{ij})}{\sum_{s=1}^{p} \Lambda_{sj} + \tau_j}.$$

Proof. Similar to proof of Lemma 2.3.2. □

We suppose that for each pair of groups i and k of addicts, $\lambda_i > 0$, and there exists a shooting gallery j_0 with:

$$P_{ij_0}(1-\phi_{ij_0})\Lambda_{kj_0} > 0.$$

This ensures that every group of addicts can transmit the infection forwards.

We are now in a position to complete the proof of Theorem 3.1.1, namely if $R_0 \leq 1$ then the only equilibrium is the disease-free equilibrium. We shall prove this by contradiction. Suppose that $R_0 \leq 1$ and there is another solution with some $\pi^*_{hi_0} = K_{i_0} > 0$. Then from the equilibrium solutions (3.4) we deduce that each of:

$$\pi^*_{h_1 i_0}, \quad \pi^*_{h_2 i_0}, \quad \pi^*_{y i_0}, \quad \text{and} \quad \pi^*_{z i_0},$$

is strictly positive. From the equilibrium versions of equations (2.1) and (2.2) we deduce that $\pi^*_{x i_0} > 0$ and $\pi^*_{x_1 i_0} > 0$. Also, from the equilibrium equations (3.4) we

deduce that for any $j = 1, 2, \ldots, q$:

$$\beta^*_{h_1 j}, \quad \beta^*_{h_2 j}, \quad \text{and} \quad \beta^*_{yj},$$

are all strictly positive.

Next from the equilibrium versions of equation (2.3) and (2.4) we deduce that for any other group i of addicts $\pi^*_{h_1 i}$ and $\pi^*_{h_2 i}$ are also strictly positive hence so is π^*_{hi}. Then using equation (3.5):

$$\pi^*_{hi} < \sum_{k=1}^{p} Q^*_{ik} \pi^*_{hk} \qquad \text{for} \quad i = 1, 2, \ldots p.$$

Write $\boldsymbol{\pi}^*_h = (\pi^*_{h_1}, \pi^*_{h_2}, \ldots, \pi^*_{h_p})$. Hence there exists $\epsilon > 0$ such that:

$$\mathbf{Q}^* \boldsymbol{\pi}^*_h > (1 + \epsilon) \boldsymbol{\pi}^*_h,$$

so

$$\mathbf{Q}^{*2} \boldsymbol{\pi}^*_h > (1 + \epsilon) \mathbf{Q}^* \boldsymbol{\pi}^*_h > (1 + \epsilon)^2 \boldsymbol{\pi}^*_h.$$

Similarly,

$$\mathbf{Q}^{*3} \boldsymbol{\pi}^*_h > (1 + \epsilon)^3 \boldsymbol{\pi}^*_h.$$

Hence,

$$\mathbf{Q}^{*n} \boldsymbol{\pi}^*_h > (1 + \epsilon)^n \boldsymbol{\pi}^*_h,$$

arguing by induction, so

$$|\mathbf{Q}^{*n}\boldsymbol{\pi}_h^*| > (1+\epsilon)^n|\boldsymbol{\pi}_h^*|.$$

Therefore, as we can define a norm $\|\mathbf{A}\|$ on the space of $s \times t$ matrices by,

$$\|\mathbf{A}\| = \sup\{|\mathbf{A}x| : |x| = 1\} = \sup\left\{\frac{|\mathbf{A}x|}{|x|}, x \neq 0\right\},$$

we obtain

$$\begin{aligned}\|\mathbf{Q}^{*n}\| &= \sup_{\mathbf{x}\neq 0}\left\{\frac{|\mathbf{Q}^{*n}\mathbf{x}|}{|\mathbf{x}|}\right\}, \\ &\geq \frac{|\mathbf{Q}^{*n}\boldsymbol{\pi}_h^*|}{|\boldsymbol{\pi}_h^*|}, \\ &> (1+\epsilon)^n,\end{aligned}$$

and so $\|\mathbf{Q}^{*n}\|^{1/n} \geq (1+\epsilon)$. As $n \longrightarrow \infty$, $\|\mathbf{Q}^{*n}\|^{1/n} \longrightarrow R_0$, the spectral radius of $\mathbf{Q}^*$. Hence $R_0 \geq (1+\epsilon) > 1$. This contradicts $R_0 \leq 1$. We deduce that we must have $\pi_{hi}^* = 0$ for each group i of addicts. Thus $K_i = 0$ for each group i. The equilibrium solutions (3.4), then imply that $\pi_{h_1 i}^*$, $\pi_{h_2 i}^*$, π_{yi}^* and π_{zi}^* are all zero for each group i of addicts and $\beta_{h_1 j}^*$, $\beta_{h_2 j}^*$ and β_{yj}^* are zero for each shooting gallery j.

The equilibrium version of (2.1) then implies that $\pi_{xi}^* = 1$ for each group i of addicts and the equilibrium of (2.2) then implies that $\pi_{x_1 i}^* = 0$ for each group i of addicts. Thus if $R_0 \leq 1$ any equilibrium solution must be the disease-free equilibrium.

The next theorem answers the question of what happens when $0 \leq R_0 \leq 1$.

In this case we shall show that when R_0 takes the values between 0 and 1 inclusive HCV will die out in each group of addicts and needles in each shooting gallery.

Theorem 3.1.4. *The disease will ultimately die out whatever the initial conditions if* $R_0 \leq 1$.

Proof. The strategy we use to prove this theorem involves a number of steps. First we note that $\pi_{hi} = \pi_{h_1 i} + \pi_{h_2 i}$ represents the proportion of acutely infected addicts in group i, and, for the disease to die out, we expect that $\pi_{hi}(t) \longrightarrow 0$ as $t \longrightarrow \infty$ for each i. To establish this, we replace the differential equation for each π_{hi}, in which the right-hand side is complicated and includes many of the other unknown variables, with a differential inequality that involves only π_{hi} and $\pi_{hk}^{\infty} = \limsup_{t\to\infty} \pi_{hk}(t)$, $k = 1, 2, \ldots p$. For each i and j, we define

$$\begin{aligned}
\pi_{h_2 i}^{\infty} &= \limsup_{t\to\infty} \pi_{h_2 i}(t), \qquad \pi_{yi}^{\infty} = \limsup_{t\to\infty} \pi_{yi}(t), \qquad \pi_{zi}^{\infty} = \limsup_{t\to\infty} \pi_{zi}(t), \\
\beta_{h_1 j}^{\infty} &= \limsup_{t\to\infty} \beta_{h_1 j}(t), \qquad \beta_{h_2 j}^{\infty} = \limsup_{t\to\infty} \beta_{h_2 j}(t), \qquad \beta_{yj}^{\infty} = \limsup_{t\to\infty} \beta_{yj}(t).
\end{aligned}$$

To obtain the differential inequality for each π_{hi}, we must first show that π_{yi}^{∞}, π_{zi}^{∞}, $\beta_{h_1 j}^{\infty}$, $\beta_{h_2 j}^{\infty}$ and β_{yj}^{∞} can all be bounded above by expressions involving $\pi_{h_1 k}^{\infty}$ and $\pi_{h_2 k}^{\infty}$ $k = 1, 2, \ldots p$. An identity connecting π_{hk}^{∞} with $\pi_{h_1 k}^{\infty}$ and $\pi_{h_2 k}^{\infty}$ then leads to the differential inequality from which we obtain an upper bound for $\pi_{hi}(t)$ in terms of π_{hk}^{∞}, $k = 1, 2, \ldots p$ This upper bound then leads to the contradiction that $R_0 > 1$ if it is assumed that $\pi_{hi}^{\infty} > 0$ for some i.

Now we aim to prove several results that give upper bounds on the limit supre-

mum of each group i of addicts and shooting gallery j in terms of $\pi^{\infty}_{h_1 i}$ or $\pi^{\infty}_{h_2 i}$. From equation (2.3) and equation (2.4) we can express the link between $\pi^{\infty}_{h_1 i}$ and $\pi^{\infty}_{h_2 i}$. Arguing as in the model of Corson et al. (2012) and applying this result will complete our proof. We have the following:

Lemma 3.1.5. $\pi^{\infty}_{yi} \leq \frac{\sigma}{\mu}\, \pi^{\infty}_{h_1 i}$.

Proof. Equation (2.5) gives:

$$\frac{d}{dt}\pi_{yi} = \sigma\pi_{h_1 i} - \mu\pi_{yi}.$$

As we assume that $\pi^{\infty}_{h_1 i}$ is the lim sup of $\pi_{h_1 i}$, then $\pi^{\infty}_{h_1 i} + \epsilon \geq \pi_{h_1 i}$ for $\epsilon > 0$ and $t \geq t_0(\epsilon)$.

$$\begin{aligned}\frac{d}{dt}\left[\pi_{yi}\; e^{\mu t}\right] &= \sigma\pi_{h_1 i}\; e^{\mu t},\\ &\leq \sigma(\pi^{\infty}_{h_1 i} + \epsilon)\; e^{\mu t}, \qquad \forall\; t \geq t_0(\epsilon) \;\text{ and }\; \epsilon > 0.\end{aligned}$$

Integrating over $[t_0(\epsilon), t]$, we deduce that:

$$\begin{aligned}\pi_{yi}(t) &\leq \pi_{yi}(t_0(\epsilon))\; e^{[(-\mu)(t-t_0(\epsilon))]} + \sigma(\pi^{\infty}_{h_1 i} + \epsilon)\left[\frac{1 - e^{[(-\mu)(t-t_0(\epsilon))]}}{\mu}\right],\\ &\leq \epsilon + \frac{\sigma}{\mu}(\pi^{\infty}_{h_1 i} + \epsilon), \qquad \forall\; t \geq t_1(\epsilon) > t_0(\epsilon).\end{aligned}$$

Letting $t \longrightarrow \infty$ and taking the lim sup and choosing $\epsilon_1 = \frac{\epsilon}{\mu}(\mu + \sigma)$, we have the following:

$$\pi^{\infty}_{yi} \leq \frac{\sigma}{\mu}\pi^{\infty}_{h_1 i} + \epsilon_1.$$

So, the result follows as ϵ_1 is positive and arbitrary. Using a similar argument it is

straightforward to show that:

$$\begin{aligned}
\pi_{zi}^{\infty} &\leq \frac{\sigma\alpha}{\mu}\pi_{h_2 i}^{\infty}, \\
\beta_{h_1 j}^{\infty} &\leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_1 i}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}, \\
\beta_{h_2 j}^{\infty} &\leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_2 i}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}, \\
\beta_{yj}^{\infty} &\leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi_{yi}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}.
\end{aligned}$$

□

Define $\pi_{hk} = \pi_{h_1 k} + \pi_{h_2 k}$. π_{hk} represents the proportion of addicts in group k who are infected and in the acute phase.

Lemma 3.1.6. *For each $i = 1, 2, \ldots p$:*

$$\pi_{hi}^{\infty} = \frac{\pi_{h_1 i}^{\infty}}{1-\delta} = \frac{\pi_{h_2 i}^{\infty}}{\delta}.$$

Proof. Using equations (2.3) and (2.4) we are able to find the relationship between $\pi_{h_1 i}^{\infty}$ and $\pi_{h_2 i}^{\infty}$.

$$\frac{d}{dt}\Big(\frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}\Big) = -(\mu+\sigma)\Big(\frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}\Big).$$

Hence

$$\Big(\frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}\Big) = \Big(\frac{\pi_{h_1 i}(0)}{1-\delta} - \frac{\pi_{h_2 i}(0)}{\delta}\Big)\exp(-(\mu+\sigma)t).$$

Thus, $\left(\frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}\right) \longrightarrow 0$ as $t \longrightarrow \infty$. Hence given $\epsilon > 0$ there exists t_0 such that for $t \geq t_0$:

$$(1-\delta)\pi_{h_2 i} \leq (1-\delta)\pi^{\infty}_{h_2 i} + \epsilon/2,$$

and

$$\delta\pi_{h_1 i} - (1-\delta)\pi_{h_2 i} \leq \epsilon/2.$$

So

$$\delta\pi_{h_1 i} \leq (1-\delta)\pi^{\infty}_{h_2 i} + \epsilon.$$

Hence,

$$\delta\pi^{\infty}_{h_1 i} \leq (1-\delta)\pi^{\infty}_{h_2 i} + \epsilon.$$

Since $\epsilon > 0$ is arbitrary, then:

$$\delta\pi^{\infty}_{h_1 i} \leq (1-\delta)\pi^{\infty}_{h_2 i}.$$

A similar argument shows that:

$$(1-\delta)\pi^{\infty}_{h_2 i} \leq \delta\pi^{\infty}_{h_1 i}.$$

Hence, we deduce the following:

$$\delta\pi^{\infty}_{h_1 i} = (1-\delta)\pi^{\infty}_{h_2 i}.$$

Recall that $\pi_{hi} = \pi_{h_1 i} + \pi_{h_2 i}$, then:

$$\begin{aligned} \pi^{\infty}_{hi} &\leq \pi^{\infty}_{h_1 i} + \pi^{\infty}_{h_2 i} = \pi^{\infty}_{h_1 i}\left(1 + \frac{\delta}{1-\delta}\right), \\ &\leq \frac{\pi^{\infty}_{h_1 i}}{1-\delta}\ , \\ (1-\delta)\pi^{\infty}_{hi} &\leq \pi^{\infty}_{h_1 i}. \end{aligned} \tag{3.7}$$

However,

$$\begin{aligned} (1-\delta)\pi_{hi} &= (1-\delta)(\pi_{h_1 i} + \pi_{h_2 i}), \\ &= \pi_{h_1 i} + (1-\delta)\pi_{h_2 i} - \delta\pi_{h_1 i}, \\ \pi_{h_1 i} &= (1-\delta)\pi_{hi} + \delta\pi_{h_1 i} - (1-\delta)\pi_{h_2 i}. \end{aligned}$$

Hence given $\epsilon > 0$ exists t_1 such that for $t \geq t_1$:

$$\begin{aligned} (1-\delta)\pi_{hi} &\leq (1-\delta)\pi^{\infty}_{hi} + \frac{\epsilon}{2}, \\ \delta\pi_{h_1 i} - (1-\delta)\pi_{h_2 i} &\leq \frac{\epsilon}{2}, \end{aligned}$$

$$\pi_{h_1 i} \leq (1-\delta)\pi^{\infty}_{hi} + \epsilon,$$

so

$$\pi^{\infty}_{h_1 i} \leq (1-\delta)\pi^{\infty}_{hi} + \epsilon.$$

Since $\epsilon > 0$ is arbitrary, then:

$$\pi^{\infty}_{h_1 i} \leq (1-\delta)\pi^{\infty}_{hi}.$$

Hence

$$\pi^{\infty}_{hi} \leq \frac{\pi^{\infty}_{h_1 i}}{1-\delta}.$$

Putting this together with (3.7) we deduce:

$$\pi^{\infty}_{hi} = \frac{\pi^{\infty}_{h_1 i}}{1-\delta} = \frac{\pi^{\infty}_{h_2 i}}{\delta}.$$

□

Now, we have:

$$\begin{aligned}\frac{d}{dt}\pi_{hi} &= \sum_{j=1}^{q}\big(1-\pi_{hi}-\pi_{yi}-\pi_{zi}\big)\lambda_i P_{ij}(1-\phi_{ij}) \\ &\qquad (\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}) - (\mu+\sigma)\pi_{hi}.\end{aligned}$$

Hence given $\epsilon > 0$, there exists $t_2 \geq t_0$ such that for $t_2 \leq t$:

$$\frac{d}{dt}\pi_{hi} \leq (1-\pi_{hi})\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^{\infty}_{h_1 j}+\beta^{\infty}_{h_2 j})+\alpha_y\beta^{\infty}_{yj}\big) - (\mu+\sigma)\pi_{hi}+\epsilon,$$

$$
\begin{aligned}
&\leq (1-\pi_{hi})\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij}) \\
&\qquad \frac{\alpha_h(\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{h_1k}+\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{h_2k})+\alpha_y\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{yk}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j} \\
&\qquad\qquad -(\mu+\sigma)\pi_{hi}+\epsilon, \\
&\leq (1-\pi_{hi})\left[\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\Big(\alpha_h+\alpha_y\frac{\sigma}{\mu}(1-\delta)\Big)\right. \\
&\qquad \left.\left(\frac{\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{hk}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}+\epsilon\right)\right]-(\mu+\sigma)\pi_{hi}. \\
&= (\mu+\sigma)\left[(1-\pi_{hi})\left(\sum_{j=1}^{q}\frac{\lambda_i P_{ij}(1-\phi_{ij})\xi\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{hk}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}+\epsilon_{1i}\right)-\pi_{hi}\right],
\end{aligned}
$$

$$
= (\mu+\sigma)\left[(1-\pi_{hi})\left(\sum_{k=1}^{p}Q^{*}_{ik}\pi^{\infty}_{hk}+\epsilon_{1i}\right)-\pi_{hi}\right],
$$

where $\epsilon_1=\epsilon\xi\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})$, and $\mathbf{Q}^{*}$ is a matrix defined earlier. Recall that R_0 is the spectral radius of $\mathbf{Q}^{*}$ and $R_0=\rho(\mathbf{Q}^{*})\leq 1$. Thus we have:

$$
\frac{d}{dt}\pi_{hi} \leq (\mu+\sigma)\left[\Big(\sum_{k=1}^{p}Q^{*}_{ik}\pi^{\infty}_{hk}+\epsilon_{1i}\Big)-\pi_{hi}\Big(1+\sum_{k=1}^{p}Q^{*}_{ik}\pi^{\infty}_{hk}+\epsilon_{1i}\Big)\right].
$$

Hence,

$$
\pi^{\infty}_{hi}\leq\frac{\sum_{k=1}^{p}Q^{*}_{ik}\pi^{\infty}_{hk}+\epsilon_{1i}}{1+\sum_{k=1}^{p}Q^{*}_{ik}\pi^{\infty}_{hk}+\epsilon_{1i}}.
$$

As ϵ is arbitrary hence letting $\epsilon\longrightarrow 0$ and $\epsilon_{1i}\longrightarrow 0$ we deduce that:

$$
\pi^{\infty}_{hi} \leq \frac{\sum_{k=1}^{p}Q^{*}_{ik}\pi^{\infty}_{hk}}{1+\sum_{k=1}^{p}Q^{*}_{ik}\pi^{\infty}_{hk}}.
$$

Now, we suppose that some $\pi^{\infty}_{hi}>0$ and that for each pair of groups i and k of

addicts, $\lambda_i > 0$ and there exists a shooting gallery j_0 with:

$$P_{ij_0}(1 - \phi_{ij_0})\Lambda_{kj_0} > 0. \tag{3.8}$$

Then $\sum_{k=1}^{p} Q^*_{ik}\pi^\infty_{hk} > 0$ so there exists $\epsilon_2 > 0$ such that:

$$\pi^\infty_{hi}(1 + \epsilon_2) \leq \sum_{k=1}^{p} Q^*_{ik}\pi^\infty_{hk},$$

(i.e. in vector notation)

$$\boldsymbol{\pi}^\infty_h(1 + \epsilon_2) \;\; \leq \;\; \boldsymbol{Q}^*\boldsymbol{\pi}^\infty_h,$$

where $\boldsymbol{\pi}^\infty_h = (\pi^\infty_{h1}, \pi^\infty_{h2}, \ldots, \pi^\infty_{hp}) \neq \mathbf{0}$, then:

$$\begin{aligned}
\boldsymbol{\pi}^\infty_h(1 + \epsilon_2)^2 &\leq \boldsymbol{Q}^{*2}\boldsymbol{\pi}^\infty_h, \\
\boldsymbol{\pi}^\infty_h(1 + \epsilon_2)^3 &\leq \boldsymbol{Q}^{*3}\boldsymbol{\pi}^\infty_h, \\
\mathbf{0} < \boldsymbol{\pi}^\infty_h(1 + \epsilon_2)^n &\leq \boldsymbol{Q}^{*n}\boldsymbol{\pi}^\infty_h.
\end{aligned}$$

Thus,

$$\mid \boldsymbol{\pi}^\infty_h \mid (1 + \epsilon_2)^n \;\; \leq \;\; \parallel \boldsymbol{Q}^{*n} \parallel \;\; \mid \boldsymbol{\pi}^\infty_h \mid \qquad \text{where} \quad \mid \boldsymbol{\pi}^\infty_h \mid \neq 0.$$

Hence,

$$\begin{aligned}
\parallel \boldsymbol{Q}^{*n} \parallel &\geq (1 + \epsilon_2)^n, \\
\parallel \boldsymbol{Q}^{*n} \parallel^{\frac{1}{n}} &\geq (1 + \epsilon_2),
\end{aligned}$$

letting $n \longrightarrow \infty$, we deduce that:

$$R_0 = \rho(\mathbf{Q}^*) \geq 1 + \epsilon_2 > 1.$$

This contradicts that $R_0 \leq 1$, thus if $R_0 \leq 1$ then each $\pi_{hk}^{\infty} = 0$. It is straightforward to show that:

$$\pi_{h_1k}^{\infty}, \quad \pi_{h_2k}^{\infty}, \quad \pi_{yk}^{\infty}, \quad \pi_{zk}^{\infty}, \quad \beta_{h_1k}^{\infty}, \quad \beta_{h_2k}^{\infty} \quad \text{and} \quad \beta_{yk}^{\infty},$$

are all zero and hence:

$$\pi_{x_1k}^{\infty} = 0 \qquad \text{and} \qquad \pi_{xk}^{\infty} = 1.$$

So the system approaches the disease-free equilibrium as $t \longrightarrow \infty$. Therefore, we must have:

$$\lim_{t\to\infty} \pi_{h_1k}(t) = \lim_{t\to\infty} \pi_{h_2k}(t) = \lim_{t\to\infty} \pi_{yk}(t) = \lim_{t\to\infty} \pi_{zk}(t) = \lim_{t\to\infty} \beta_{h_1k}(t) = \lim_{t\to\infty} \beta_{h_2k}(t) = \lim_{t\to\infty} \beta_{yk}(t) = 0.$$

This completes the proof of the global stability of the disease-free equilibrium when $R_0 \leq 1$. Further analysis will show the existence of a non-zero endemic equilibrium solution when R_0 exceeds unity.

Theorem 3.1.7. *If $R_0 \leq 1$, then there is only the disease-free equilibrium solution to the system.*

Proof. Actually this follows from the results above, and we have shown it before, but

we can show it directly. As we mentioned earlier that:

$$\begin{aligned}
\pi^*_{hi} &= \pi^*_{h_1 i} + \pi^*_{h_2 i}, \\
&= \frac{1}{\mu+\sigma}\Big(1 - \pi^*_{hi}\Big(1 + \frac{\sigma}{\mu}(1-\delta) + \frac{\sigma}{\mu}\delta\alpha\Big)\Big) \\
&\qquad \sum_{j=1}^{q} \lambda_i P_{ij}(1-\phi_{ij}) \frac{\sum_{k=1}^{p} \Lambda_{kj}\pi^*_{hk}}{\sum_{k=1}^{p}\Lambda_{kj} + \tau_j}\Big(\alpha_h + \alpha_y \frac{\sigma}{\mu}(1-\delta)\Big), \\
&= (1 - \pi^*_{hi}P)\frac{\sum_{j=1}^{q}\xi\lambda_i P_{ij}(1-\phi_{ij})\sum_{k=1}^{p}\Lambda_{kj}}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\ \pi^*_{hk}, \\
&= (1 - \pi^*_{hi}P)\sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}, \qquad (3.9)
\end{aligned}$$

where $P = 1 + \frac{\sigma}{\mu}(1-\delta) + \frac{\sigma}{\mu}\delta\alpha$. Then we have:

$$\pi^*_{hi} = \frac{\sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}}{1 + P\sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}} = \frac{x_i}{1+Px_i},$$

where

$$x_i = \sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk} = \sum_{k=1}^{p} Q^*_{ik}\frac{x_k}{1+Px_k}.$$

This is considered as the key defining equation. We can write this as:

$$\boldsymbol{x} = \mathbf{M}(\boldsymbol{x})\boldsymbol{x}, \qquad (3.10)$$

such that $\boldsymbol{x}$ is a vector $\boldsymbol{x} = (x_1, x_2, \ldots, x_p)$ and $\mathbf{M}$ is a matrix with:

$$M_{ik}(\boldsymbol{x}) = \frac{Q^*_{ik}}{1+Px_k}.$$

Note that all $M_{ik} \geq 0$ and $M_{ik}(\boldsymbol{x})$ is decreasing in $\boldsymbol{x}$. Also, $\mathbf{M}(\mathbf{0}) = \mathbf{Q}^*$. We want to show that if $R_0 \leq 1$, then the only non-negative solution $\boldsymbol{x}$ to this equation is $\boldsymbol{x} = \mathbf{0}$

(i.e. $x_1 = x_2 = \cdots = x_p = 0$). This will be done following a similar argument as in the proof of Lemma 3.1 of Greenhalgh (1990).

Let us suppose that $\boldsymbol{x}$ is a non-zero (positive) solution to our equation $\boldsymbol{x} = \mathbf{M}(\boldsymbol{x})\boldsymbol{x}$, where $x_i \geq 0$ for $i = 1, 2, \ldots, p$ and some $x_j > 0$. We have previously assumed that for each pair of groups i and k of addicts $\lambda_i > 0$ and there exists a shooting gallery j_0 with $P_{ij_0}(1 - \phi_{ij_0})\Lambda_{kj_0} > 0$. Hence, $Q^*_{ik} > 0$ for each i, k:

$$\begin{aligned} M_{ik}(\boldsymbol{x}) &= \frac{Q^*_{ik}}{1 + Px_k} < Q^*_{ik} = M_{ik}(\mathbf{0}), \\ \boldsymbol{x}_i &= \sum_{k=1}^{p} M_{ik}(\boldsymbol{x})x_k \leq \sum_{k=1}^{p} M_{ik}(\mathbf{0})x_k = \big(\mathbf{M}(\mathbf{0})\boldsymbol{x}\big)_i. \end{aligned}$$

Moreover there is strict inequality here as some $x_i > 0$. Hence:

$$\boldsymbol{x} < \mathbf{M}(\mathbf{0})\boldsymbol{x},$$

so, there exists $\epsilon > 0$ such that:

$$\begin{aligned} \boldsymbol{x}(1 + \epsilon) &< \mathbf{M}(\mathbf{0})\boldsymbol{x}, \\ \boldsymbol{x}(1 + \epsilon)^2 &< \mathbf{M}(\mathbf{0})\boldsymbol{x}(1 + \epsilon) < \mathbf{M}^2(\mathbf{0})\boldsymbol{x}. \end{aligned}$$

Similarly:

$$\begin{aligned} \boldsymbol{x}(1 + \epsilon)^3 &< \mathbf{M}^3(\mathbf{0})\boldsymbol{x}, \\ \boldsymbol{x}(1 + \epsilon)^n &< \mathbf{M}^n(\mathbf{0})\boldsymbol{x}. \end{aligned}$$

Take the norm for the vectors:

$$\begin{aligned} |\boldsymbol{x}|(1+\epsilon)^n &< \| \mathbf{M}^n(\mathbf{0}) \| \ |\boldsymbol{x}|, \\ (1+\epsilon)^n &< \| \mathbf{M}^n(\mathbf{0}) \|, \\ 1+\epsilon &< \| \mathbf{M}^n(\mathbf{0}) \|^{1/n} . \end{aligned}$$

Take the limit as n goes to infinity $\lim_{n\to\infty} \| \mathbf{M}^n(\mathbf{0}) \|^{1/n} = \lim_{n\to\infty} \| \mathbf{Q}^{*n} \|^{1/n} = R_0$. Therefore we deduce that:

$$1+\epsilon \leq R_0,$$

this is a contradiction. □

In this following section, we prove that there is at least one positive solution equilibrium if $R_0 > 1$. The next theorem is proved by a similar technique to Theorem 2 of the model by Greenhalgh (1993). We use C to represent the cone of positive vectors:

$$C = \{(x_1, x_2, \ldots, x_p) : x_1 \geq 0, x_2 \geq 0, \ldots, x_p \geq 0\}.$$

C is clearly a cone: if $\boldsymbol{x} \in C$ then $\alpha\boldsymbol{x} \in C$ for all $\alpha > 0$.

Theorem 3.1.8. *Assume that $R_0 > 1$. Then the equation (3.10) has at least one positive non-zero solution corresponding to an equilibrium.*

We use Theorem 1.6 of Gatica & Smith (1977) applied to the operator $T : C \longrightarrow C$ given by the equation:

$$T(\boldsymbol{x}) = \mathbf{M}(\boldsymbol{x})\boldsymbol{x}. \tag{3.11}$$

This theorem states:

Theorem 3.1.9. *Let $T : C \longrightarrow C$ be a compact continuous operator acting on a Banach space $\boldsymbol{X}$ where $\boldsymbol{X} = \mathbb{R}^p$, such that $T(\boldsymbol{0}) = \boldsymbol{0}$ and T is Fréchet differentiable at $\boldsymbol{x}$=$\boldsymbol{0}$ in the direction of the cone. Assume that T satisfies:*

(a) *$T'(\boldsymbol{0})$, the Fréchet derivative of T at $\boldsymbol{x}$=$\boldsymbol{0}$, has an eigenvector $\boldsymbol{x} \in C$ corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C; and*

(b) *there exists an $R > 0$ such that if $\boldsymbol{x} \in C$ with $|\boldsymbol{x}| = R$ and $T\boldsymbol{x} = \mu\boldsymbol{x}$ then $\mu \leq 1$. Then T has a non-zero fixed point $\boldsymbol{x}_0 \in C$ with $|\boldsymbol{x_0}| \leq R$.*

In order to apply this theorem we need to prove the following:

(a) *$T : C \longrightarrow C$ is a continuous compact operator;*

(b) *$T'(\boldsymbol{0})$ has an eigenvector $\boldsymbol{x} \in C$ corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C; and*

(c) *there exists an $R > 0$ such that if $\boldsymbol{x} \in C$ with $|\boldsymbol{x}| = R$ and $T\boldsymbol{x} = \mu\boldsymbol{x}$ then $\mu \leq 1$.*

To prove this theorem, we need to prove the following results:

Lemma 3.1.10. *$T(\boldsymbol{x})$:$C \longrightarrow$ C is continuous in $\boldsymbol{x}$ for all $\boldsymbol{x} > 0$.*

Proof. We shall prove that given $\epsilon > 0$ there exists $\delta > 0$ such that for $|\boldsymbol{x} - \tilde{\boldsymbol{x}}| < \delta$, $|T(\boldsymbol{x}) - T(\tilde{\boldsymbol{x}})| < \epsilon$. As for each i and k $M_{ik}(x_k)$ is continuous in x_k, we know that there exists $\delta > 0$ such that for $|\boldsymbol{x} - \tilde{\boldsymbol{x}}| < \delta$:

$$\max\{|M_{11}x_1 - \tilde{M}_{11}\tilde{x}_1|, |M_{12}x_2 - \tilde{M}_{12}\tilde{x}_2|, \ldots, |M_{1p}x_p - \tilde{M}_{1p}\tilde{x}_p|, \ldots, |M_{pp}x_p - \tilde{M}_{pp}\tilde{x}_p|\} < \frac{\epsilon}{p\sqrt{p}}.$$

Then we can use the triangle inequality:

$$\begin{aligned} |M_{11}x_1 - \tilde{M}_{11}\tilde{x}_1 + \cdots + M_{1p}x_p - \tilde{M}_{1p}\tilde{x}_p| &< \frac{\epsilon}{p\sqrt{p}} + \frac{\epsilon}{p\sqrt{p}} + \cdots + \frac{\epsilon}{p\sqrt{p}}, \\ &= \frac{p\epsilon}{p\sqrt{p}}, \\ &= \frac{\epsilon}{\sqrt{p}}. \end{aligned}$$

Similarly for every row in the matrix $\mathbf{M}$ i.e. for row r, where $r = 1, 2, \ldots, p$

$$|M_{r1}x_1 - \tilde{M}_{r1}\tilde{x}_1 + \ldots, + M_{rp}x_p - \tilde{M}_{rp}\tilde{x}_p| < \frac{\epsilon}{\sqrt{p}}.$$

For $|\boldsymbol{x} - \tilde{\boldsymbol{x}}| < \delta$, we have from equation (3.11) that:

$$|T(\boldsymbol{x}) - T(\tilde{\boldsymbol{x}})| = |\mathbf{M}(\boldsymbol{x})\boldsymbol{x} - \mathbf{M}(\tilde{\boldsymbol{x}})\tilde{\boldsymbol{x}}|.$$

For $r = 1, 2, \ldots p$ define:

$$B_r = M_{r1}x_1 - \tilde{M}_{r1}\tilde{x}_1 + M_{r2}x_2 - \tilde{M}_{r2}\tilde{x}_2 + \cdots + M_{rp}x_p - \tilde{M}_{rp}\tilde{x}_p.$$

From the definition of the norm $|.|$ of a vector in $\mathbb{R}^p$ we deduce that:

$$\begin{aligned} \Big| \Big(& M_{11}x_1 - \tilde{M}_{11}\tilde{x}_1 + M_{12}x_2 - \tilde{M}_{12}\tilde{x}_2 + \cdots + M_{1r}x_r - \tilde{M}_{1r}\tilde{x}_r, \\ & M_{21}x_1 - \tilde{M}_{21}\tilde{x}_1 + M_{22}x_2 - \tilde{M}_{22}\tilde{x}_2 + \cdots + M_{2r}x_r - \tilde{M}_{2r}\tilde{x}_r, \\ & \cdots \\ & \vdots \qquad\qquad \vdots \qquad\qquad \vdots, \\ & , M_{p1}x_1 - \tilde{M}_{p1}\tilde{x}_1 + M_{p2}x_2 - \tilde{M}_{p2}\tilde{x}_2 + \cdots + M_{pr}x_r - \tilde{M}_{pr}\tilde{x}_r \Big) \Big| \end{aligned}$$

$$= \sqrt{B_1^2 + B_2^2 + \cdots + B_p^2}\ ,$$
$$\leq \sqrt{\frac{\epsilon^2}{p} + \frac{\epsilon^2}{p} + \cdots + \frac{\epsilon^2}{p}}\ ,$$
$$= \epsilon.$$

Therefore, we deduce that:

$$|T(\boldsymbol{x}) - T(\tilde{\boldsymbol{x}})| < \epsilon.$$

Thus we have shown that $|T(\boldsymbol{x}) - T(\tilde{\boldsymbol{x}})| < \epsilon$, for $|\boldsymbol{x} - \tilde{\boldsymbol{x}}| < \delta$. This implies that $T(\boldsymbol{x})$ is continuous in $\boldsymbol{x}$. □

Lemma 3.1.11. *T(**x**):C⟶ C is bounded.*

Proof. We need to show that there exists K such that $\Big[\mathbf{M}(\boldsymbol{x})\boldsymbol{x}\Big]_i = \sum_{k=1}^{p} M_{ik}(\boldsymbol{x})x_k \leq K$ for all $i = 1, 2, \ldots p$. It is sufficient to show that each $M_{ik}(\boldsymbol{x})x_k$ is bounded in C. It is obvious that these quantities are bounded below by zero, because as mentioned earlier $M_{ik}(\boldsymbol{x}) \geq 0$. The term $M_{ik}(\boldsymbol{x})x_k$ is given by:

$$\left[\frac{Q_{ik}^*}{1 + \big(1 + \frac{\sigma}{\mu}(1-\delta) + \frac{\sigma}{\mu}\delta\alpha\big)x_k}\right]x_k. \tag{3.12}$$

We know that Q_{ik}^* and all other parameters are fixed and finite. Thus, we can re-write the expression (3.12) as follows:

$$M_{ik}(\boldsymbol{x})x_k = \left(\frac{A}{1 + Bx_k}\right)x_k,$$

where A and B are constants independent of x_k. Since

$$\frac{x_k}{1 + Bx_k} \leq \frac{1}{B},$$

we have that

$$M_{ik}(\boldsymbol{x})x_k \leq \frac{A}{B}.$$

Choosing $K = \frac{pA}{B}$ will complete the proof of this result. □

In normed space a linear operator which is continuous must be bounded and if such an operator is bounded it must also be continuous (Collatz, 1966). We know that $T(\boldsymbol{x}) = \mathbf{M}(\boldsymbol{x})\boldsymbol{x}$ is a bounded continuous operator in $\mathbb{R}^p$ which is a finite dimensional vector space. In a finite dimensional space the range of T is compact (Oden & Demkowicz, 2010). Hence, $T(\boldsymbol{x})$ is a continuous compact operator.

We have shown that the operator $T(\boldsymbol{x})$ is a continuous compact operator, and now we wish to show that $T(\boldsymbol{x})$ is Fréchet differentiable at $\boldsymbol{x} = \mathbf{0}$ in the direction of the cone C. The operator $T(\boldsymbol{x})$ is Fréchet differentiable at $\boldsymbol{x} = \mathbf{0}$ in the direction of the cone C if there is a bounded linear operator $T'(\mathbf{0})$ such that

$$T(\boldsymbol{x}) = T(\mathbf{0}) + T'(\mathbf{0})(\boldsymbol{x}) + o(|\boldsymbol{x}|),$$

for all $\boldsymbol{x}$ in C (Greenhalgh, 1993). $T'(\mathbf{0})$ is called the Fréchet derivative of $T(\boldsymbol{x})$ at $\boldsymbol{x} = \mathbf{0}$ in the direction of the cone C.

Lemma 3.1.12. *$T(\boldsymbol{x})$ is Fréchet differentiable at $\boldsymbol{x} = \boldsymbol{0}$ in the direction of the cone*

C with Fréchet derivative

$$T'(\boldsymbol{O}) = \begin{bmatrix} M_{11}(\boldsymbol{O}) & M_{12}(\boldsymbol{O}) & \dots & M_{1p}(\boldsymbol{O}) \\ M_{21}(\boldsymbol{O}) & M_{22}(\boldsymbol{O}) & \dots & M_{2p}(\boldsymbol{O}) \\ \vdots & & & \vdots \\ M_{p1}(\boldsymbol{O}) & M_{p2}(\boldsymbol{O}) & \dots & M_{pp}(\boldsymbol{O}) \end{bmatrix}.$$

Proof. $T'(\mathbf{0})$ is a bounded linear operator. Let us denote $\omega(\boldsymbol{x})$ to be:

$$\omega(\boldsymbol{x}) = T(\boldsymbol{x}) - T(\mathbf{0}) - T'(\mathbf{0})(\boldsymbol{x}). \tag{3.13}$$

If T is Fréchet differentiable in the direction of the cone C, we must show that:

$$\omega(\boldsymbol{x}) = o(|\boldsymbol{x}|), \qquad \text{for all} \qquad \boldsymbol{x} \in C.$$

From equation (3.13) we deduce the following:

$$\omega(\boldsymbol{x}) = \boldsymbol{M}(\boldsymbol{x})\boldsymbol{x} - T(\mathbf{0}) - T'(\mathbf{0})(\boldsymbol{x}).$$

We mention that $\mathbf{M}(\mathbf{0}) = \mathbf{Q}^*$. Then:

$$\omega(\boldsymbol{x}) \;=\; \begin{bmatrix} M_{11}(\boldsymbol{x}) & M_{12}(\boldsymbol{x}) & \dots & M_{1p}(\boldsymbol{x}) \\ M_{21}(\boldsymbol{x}) & M_{22}(\boldsymbol{x}) & \dots & M_{2p}(\boldsymbol{x}) \\ \vdots & & & \vdots \\ M_{p1}(\boldsymbol{x}) & M_{p2}(\boldsymbol{x}) & \dots & M_{pp}(\boldsymbol{x}) \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_p \end{bmatrix}$$

$$- \begin{bmatrix} M_{11}(\mathbf{0}) & M_{12}(\mathbf{0}) & \dots & M_{1p}(\mathbf{0}) \\ M_{21}(\mathbf{0}) & M_{22}(\mathbf{0}) & \dots & M_{2p}(\mathbf{0}) \\ \vdots & & & \vdots \\ M_{p1}(\mathbf{0}) & M_{p2}(\mathbf{0}) & \dots & M_{pp}(\mathbf{0}) \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_p \end{bmatrix},$$

$$= \begin{bmatrix} M_{11}(\boldsymbol{x})x_1 + M_{12}(\boldsymbol{x})x_2 + \cdots + M_{1p}(\boldsymbol{x})x_p \\ M_{21}(\boldsymbol{x})x_1 + M_{22}(\boldsymbol{x})x_2 + \cdots + M_{2p}(\boldsymbol{x})x_p \\ \vdots \\ M_{p1}(\boldsymbol{x})x_1 + M_{p2}(\boldsymbol{x})x_2 + \cdots + M_{pp}(\boldsymbol{x})x_p \end{bmatrix}$$

$$- \begin{bmatrix} M_{11}(\mathbf{0})x_1 + M_{12}(\mathbf{0})x_2 + \cdots + M_{1p}(\mathbf{0})x_p \\ M_{21}(\mathbf{0})x_1 + M_{22}(\mathbf{0})x_2 + \cdots + M_{2p}(\mathbf{0})x_p \\ \vdots \\ M_{p1}(\mathbf{0})x_1 + M_{p2}(\mathbf{0})x_2 + \cdots + M_{pp}(\mathbf{0})x_p \end{bmatrix},$$

$$= \begin{bmatrix} \big[M_{11}(\boldsymbol{x}) - M_{11}(\mathbf{0})\big]x_1 + \big[M_{12}(\boldsymbol{x}) - M_{12}(\mathbf{0})\big]x_2 + \cdots + \big[M_{1p}(\boldsymbol{x}) - M_{1p}(\mathbf{0})\big]x_p \\ \big[M_{21}(\boldsymbol{x}) - M_{21}(\mathbf{0})\big]x_1 + \big[M_{22}(\boldsymbol{x}) - M_{22}(\mathbf{0})\big]x_2 + \cdots + \big[M_{2p}(\boldsymbol{x}) - M_{2p}(\mathbf{0})\big]x_p \\ \vdots \\ \big[M_{p1}(\boldsymbol{x}) - M_{p1}(\mathbf{0})\big]x_1 + \big[M_{p2}(\boldsymbol{x}) - M_{p2}(\mathbf{0})\big]x_2 + \cdots + \big[M_{pp}(\boldsymbol{x}) - M_{pp}(\mathbf{0})\big]x_p \end{bmatrix}.$$

Therefore, we observe that:

$$\omega(\boldsymbol{x}) = \boldsymbol{a}_1 + \boldsymbol{a}_2 + \cdots + \boldsymbol{a}_p, \qquad \text{where for} \quad r = 1, 2, \dots p,$$

$$\boldsymbol{a}_r = \begin{bmatrix} 0 \\ 0 \\ \vdots \\ A_r \\ \vdots \\ 0 \end{bmatrix},$$

with only entry A_r in the r^{th} row, where:

$$\begin{aligned} A_r &= [M_{r1}(\boldsymbol{x}) - M_{r1}(\boldsymbol{0})]x_1 + [M_{r2}(\boldsymbol{x}) - M_{r2}(\boldsymbol{0})]x_2 + \cdots + [M_{rp}(\boldsymbol{x}) - M_{rp}(\boldsymbol{0})]x_p, \\ |A_r| &\leq |M_{r1}(\boldsymbol{x}) - M_{r1}(\boldsymbol{0})|\ |x_1| + |M_{r2}(\boldsymbol{x}) - M_{r2}(\boldsymbol{0})|\ |x_2| + \cdots + |M_{rp}(\boldsymbol{x}) - M_{rp}(\boldsymbol{0})|\ |x_p|. \end{aligned}$$

Thus

$$\begin{aligned} |\omega(\boldsymbol{x})| &\leq |A_1| + |A_2| + \cdots + |A_p|, \\ &\leq |M_{11}(\boldsymbol{x}) - M_{11}(\boldsymbol{0})|\ |x_1| + |M_{12}(\boldsymbol{x}) - M_{12}(\boldsymbol{0})|\ |x_2| + \\ &\quad \cdots + |M_{p1}(\boldsymbol{x}) - M_{p1}(\boldsymbol{0})|\ |x_1| + |M_{p2}(\boldsymbol{x}) - M_{p2}(\boldsymbol{0})|\ |x_2| + \\ &\quad \cdots + |M_{pp}(\boldsymbol{x}) - M_{pp}(\boldsymbol{0})|\ |x_p|. \end{aligned}$$

Dividing by $|\boldsymbol{x}|$ we deduce the following:

$$\begin{aligned} \frac{|\omega(\boldsymbol{x})|}{|\boldsymbol{x}|} &\leq |M_{11}(\boldsymbol{x}) - M_{11}(\boldsymbol{0})|\frac{|x_1|}{|\boldsymbol{x}|} + |M_{12}(\boldsymbol{x}) - M_{12}(\boldsymbol{0})|\frac{|x_2|}{|\boldsymbol{x}|} + \\ &\quad \cdots + |M_{p1}(\boldsymbol{x}) - M_{p1}(\boldsymbol{0})|\frac{|x_1|}{|\boldsymbol{x}|} + |M_{p2}(\boldsymbol{x}) - M_{p2}(\boldsymbol{0})|\frac{|x_2|}{|\boldsymbol{x}|} + \\ &\quad \cdots + |M_{pp}(\boldsymbol{x}) - M_{pp}(\boldsymbol{0})|\frac{|x_p|}{|\boldsymbol{x}|}, \end{aligned}$$

$$\leq \sum_{i=1}^{p}\sum_{j=1}^{q}\big|M_{ij}(\boldsymbol{x}) - M_{ij}(\mathbf{0})\big|.$$

As M_{ij} is continuous at $\boldsymbol{x} = \mathbf{0}$, given $\epsilon > 0$ there exists $\delta > 0$ such that $|\boldsymbol{x}| < \delta$ implies that $\big|M_{ij}(\boldsymbol{x}) - M_{ij}(\mathbf{0})\big| < \epsilon/p^2$ for $i = 1, 2, \ldots, p$. Thus,

$$\frac{|\omega(\boldsymbol{x})|}{|\boldsymbol{x}|} < p^2\Big(\frac{\epsilon}{p^2}\Big) = \epsilon.$$

As $\epsilon > 0$ is arbitrary we deduce that

$$\omega(\boldsymbol{x}) = o(|\boldsymbol{x}|),$$

and $T(\boldsymbol{x})$ is Fréchet differentiable at $\boldsymbol{x} = \mathbf{0}$ in the direction of the cone C. □

Next we are going to prove the second part of the theorem. So, we need to show that $T'(\mathbf{0})$ has an eigenvector $\boldsymbol{x} \in C$ corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\mathbf{0})$ with corresponding eigenvector in C.

Lemma 3.1.13. *$T'(\mathbf{0})$ has an eigenvector $\boldsymbol{x} \in C$ corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\mathbf{0})$ with corresponding eigenvector in C.*

Proof. $T'(\mathbf{0})$ is a matrix with positive entries (as we know that $\mathbf{M}(\boldsymbol{x}) \geq \mathbf{0}$). We can use the *Perron-Frobenius* theory of positive matrices (Bapat & Raghavan, 1997).

This theory says that there is a positive real number r, called the Perron root or the Perron-Frobenius eigenvalue such that r is an eigenvalue of $T'(\mathbf{0})$ and any other eigenvalue, λ is strictly smaller in absolute value, $|\lambda| < r$.

Thus the spectral radius $\rho(T'(\mathbf{0})) = r$. Furthermore, there exists an eigenvector $\boldsymbol{v}$ of $T'(\mathbf{0})$ with eigenvalue r such that all components of $\boldsymbol{v}$ are positive. Therefore, if $\rho(T'(\mathbf{0})) > 1$, then $T'(\mathbf{0})$ has an eigenvector $\boldsymbol{v} \in C$ which corresponds to an eigenvalue $\omega_0 > 1$. The theory also states that there are no other eigenvalues with positive eigenvectors. So, 1 cannot be an eigenvalue of $T'(\mathbf{0})$ with corresponding eigenvector in C. This completes the proof of this result. □

We are now going to prove last condition of the theorem, which will complete the proof of Theorem 3.1.9.

Lemma 3.1.14. *There exists $R > 0$ such that if $\boldsymbol{x} \in C$ with $|\boldsymbol{x}| = R$ and $T(\boldsymbol{x}) = \mu\boldsymbol{x}$, then $\mu \leq 1$.*

Proof. Assume that $\boldsymbol{x} \in C$ with $|\boldsymbol{x}| = R$ and $T(\boldsymbol{x}) = \mu\boldsymbol{x}$. Since $T(\boldsymbol{x})$ is positive for all $\boldsymbol{x} \geq \mathbf{0}$, then we obtain that $\mu \geq 0$.

Now let $\boldsymbol{\eta} \in C$ where $\boldsymbol{\eta} = \boldsymbol{x}/R$ and $|\boldsymbol{\eta}| = 1$. Then

$$\begin{aligned} \mu\, \boldsymbol{x} &= T(\boldsymbol{x}), \\ \mu\, R\, \boldsymbol{\eta} &= T(R\, \boldsymbol{\eta}), \\ \mu\, \boldsymbol{\eta} &= \frac{1}{R} T(R\, \boldsymbol{\eta}). \end{aligned}$$

As $\mu \geq 0$ then $|\mu\boldsymbol{\eta}| = \mu|\boldsymbol{\eta}| = \mu = \frac{1}{R}|T(R\, \boldsymbol{\eta})|$. We proved earlier that $T(\boldsymbol{x})$ is a bounded compact operator, thus there is a positive constant y which is independent of R, such that: $|T(\boldsymbol{x})| \leq y$ for all $\boldsymbol{x}$ and hence:

$$\mu = \frac{1}{R}|T(R\boldsymbol{\eta})| \leq \frac{y}{R}.$$

Hence, if $R \geq y$ then we have that $\mu \leq 1$. □

We are now in position to show that the endemic equilibrium solution to our model is unique. This is obtained by using a similar argument along the lines in the proof of Theorem 3.1 of Lajmanovich & Yorke (1976), who developed a deterministic model to examine the spread of gonorrhea in an non-homogeneous population. The work of Lajmanovich and Yorke (1976) considers disease that does not confer immunity (i.e. gonorrhea) in a population divided into n groups, G_i where $i = 1, 2, \ldots n$, having constant contact rates with each other. The authors study an autonomous differential equation that models the development of the infection levels in the n groups. Using a Liapunov function, they prove a striking dichotomy: either the disease dies out or there is a unique positive equilibrium state. The main result of their work is that either the epidemic will die out naturally for every possible initial stage of the epidemic, or when this is not true and the initial number of infectives of at least one group is nonzero, the disease will remain endemic for all future time. Using the results of Lajmanovich and Yorke we shall show that any non-zero equilibrium solution must be unique. First, we need the following lemma:

Lemma 3.1.15. *Suppose that some $\pi^*_{hk} > 0$ and for each i, k, $\lambda_i > 0$ and there exists j_0 with*

$$P_{ij_0}(1 - \phi_{ij_0})\Lambda_{kj_0} > 0.$$

Then for each $i = 1, 2, \ldots p$, $\frac{1}{P} > \pi^*_{hi} > 0$, where $P = 1 + \frac{\sigma}{\mu}(1 - \delta) + \frac{\sigma}{\mu}\delta\alpha$.

Proof. Under the above conditions for i, we have:

$$\sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk} > 0.$$

Therefore,

$$\begin{aligned}\frac{1}{P} &> \pi^*_{hi} \\ &= \frac{\sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}}{1+P\sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}} > 0.\end{aligned}$$

□

Theorem 3.1.16. *If $R_0 > 1$, the system (2.1)- (2.9) has a unique endemic equilibrium.*

Proof. Let $(\tilde{\pi}^*_{h1}, \tilde{\pi}^*_{h2}, \ldots, \tilde{\pi}^*_{hp})$ and $(\pi^*_{h1}, \pi^*_{h2}, \ldots, \pi^*_{hp})$ be two distinct non-zero equilibrium solutions. This implies that $\pi^*_{hi_0} \neq \tilde{\pi}^*_{hi_0}$ for some $i_0 \in 1, 2, \ldots p$. So, $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} \neq 1$, thus either $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} > 1$ or $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} < 1$. If $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} < 1$ we can redefine our parameters to allow us to assume without loss of generality that $\tilde{\pi}^*_{h1}/\pi^*_{h1} > 1$, and moreover, that

$$\frac{\tilde{\pi}^*_{h1}}{\pi^*_{h1}} > \frac{\tilde{\pi}^*_{hj}}{\pi^*_{hj}} \quad \forall \;\; j = 2, 3, \ldots p.$$

Then, from equation (3.9) we deduce that:

$$\begin{aligned}0 &= -\tilde{\pi}^*_{h1} + (1 - P\tilde{\pi}^*_{h1})\sum_{k=1}^{p} Q^*_{ik}\tilde{\pi}^*_{hk}, \\ &= -\pi^*_{h1} + (1 - P\pi^*_{h1})\sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}.\end{aligned}$$

Now, we multiply the two sides of the first equation by $\pi^*_{h1}/\tilde{\pi}^*_{h1}$. We deduce that:

$$0 = -\pi^*_{h1} + (1 - P\tilde{\pi}^*_{h1})\sum_{k=1}^{p} Q^*_{ik}\tilde{\pi}^*_{hk}\frac{\pi^*_{h1}}{\tilde{\pi}^*_{h1}},$$

$$< \quad -\pi^*_{h1} + (1 - P\pi^*_{h1}) \sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}.$$

This is because $\frac{\tilde{\pi}^*_{hk}}{\tilde{\pi}^*_{h1}}\pi^*_{h1} \leq \tilde{\pi}^*_{hk}$ for $k = 1, 2, \ldots p$ and $1 - P\tilde{\pi}^*_{h1} < 1 - P\pi^*_{h1}$. This is a contradiction thus we cannot have two distinct non-zero equilibrium solutions. This implies that $\pi^*_{hi} = \tilde{\pi}^*_{hi}$ for $i = 1, 2, \ldots, p$. This complete the proof of existing a unique endemic equilibrium when $R_0 > 1$. □

We have examined the behaviour of our disease transmission model in the case where $R_0 \leq 1$. We have shown that this is a necessary and sufficient condition for HCV to die out among group of injecting drug users and shooting galleries. We also showed that for $R_0 > 1$ there exists a unique endemic equilibrium. We shall prove that under the condition $R_0 > 1$ the disease-free equilibrium is unstable and HCV will remain persistent in the population.

3.2 Stability of the Disease-Free Equilibrium

From mathematical and biological points of view, it is usually important to analyse the local stability of the disease-free equilibrium in both cases where $R_0 \leq 1$ and $R_0 > 1$. For $R_0 \leq 1$ we know that the disease-free equilibrium is globally asymptotically stable hence locally asymptotically stable. Now we shall show that if $R_0 > 1$ then the disease-free equilibrium is unstable.

Theorem 3.2.1. *The disease-free equilibrium is unstable if* $R_0 > 1$.

Proof. We know that for each group i of injecting drug users, $\pi_{xi} + \pi_{x_1 i} + \pi_{h_1 i} + \pi_{h_2 i} + \pi_{yi} + \pi_{zi} = 1$. Since we are only interested in stability of the system behaviour, we can reduce the system of (2.1) - (2.9) to a system which consists of equations (2.2)

- (2.9). This done by omitting the equation (2.1) from consideration, as this will not affect the final result because the equations are linearly independent. We take the remaining equations (2.2) – (2.9) and linearise the system about the disease-free equilibrium. That is we consider a small perturbation about the disease-free equilibrium, thus $\pi_{x_1 i}, \pi_{h_1 i}, \pi_{h_2 i}, \pi_{yi}, \pi_{zi}, \beta_{h_1 j}, \beta_{h_2 j}$ and β_{yj} are all small. Then we neglect the quadratic and higher order terms which are of second and higher order in small quantities. The equations become for $i = 1, 2, \ldots p$ and $j = 1, 2, \ldots q$.

$$\frac{d\pi_{x_1 i}}{dt} = \sigma(1-\alpha)\pi_{h_2 i} - \mu\pi_{x_1 i}, \tag{3.14}$$

$$\frac{d\pi_{h_1 i}}{dt} = \sum_{j=1}^{q}(1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big) - (\mu+\sigma)\pi_{h_1 i}, \tag{3.15}$$

$$\frac{d\pi_{h_2 i}}{dt} = \sum_{j=1}^{q}\delta\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big) - (\mu+\sigma)\pi_{h_2 i}, \tag{3.16}$$

$$\frac{d\pi_{yi}}{dt} = \sigma\pi_{h_1 i} - \mu\pi_{yi}, \tag{3.17}$$

$$\frac{d\pi_{zi}}{dt} = \sigma\alpha\pi_{h_2 i} - \mu\pi_{zi}, \tag{3.18}$$

$$\frac{d\beta_{h_1 j}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_1 i} - \Big(\sum_{i=1}^{p}\Lambda_{ij}+\tau_j\Big)\beta_{h_1 j}, \tag{3.19}$$

$$\frac{d\beta_{h_2 j}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_2 i} - \Big(\sum_{i=1}^{p}\Lambda_{ij}+\tau_j\Big)\beta_{h_2 j}, \tag{3.20}$$

$$\frac{d\beta_{yj}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{yi} - \Big(\sum_{i=1}^{p}\Lambda_{ij}+\tau_j\Big)\beta_{yj}. \tag{3.21}$$

Note that in the above system of differential equations (3.14)–(3.21) the π_{zi} term appears only in the fifth equation (3.18). Consider the system ignoring this equation, we have:

$$\frac{d\pi_{x_1 i}}{dt} = \sigma(1-\alpha)\pi_{h_2 i} - \mu\pi_{x_1 i}, \tag{3.22}$$

$$\frac{d\pi_{h_1 i}}{dt} = \sum_{j=1}^{q}(1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big) - (\mu+\sigma)\pi_{h_1 i}, \quad (3.23)$$

$$\frac{d\pi_{h_2 i}}{dt} = \sum_{j=1}^{q}\delta\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big) - (\mu+\sigma)\pi_{h_2 i}, \quad (3.24)$$

$$\frac{d\pi_{yi}}{dt} = \sigma\pi_{h_1 i} - \mu\pi_{yi}, \quad (3.25)$$

$$\frac{d\beta_{h_1 j}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_1 i} - \Big(\sum_{i=1}^{p}\Lambda_{ij}+\tau_j\Big)\beta_{h_1 j}, \quad (3.26)$$

$$\frac{d\beta_{h_2 j}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_2 i} - \Big(\sum_{i=1}^{p}\Lambda_{ij}+\tau_j\Big)\beta_{h_2 j}, \quad (3.27)$$

$$\frac{d\beta_{yj}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{yi} - \Big(\sum_{i=1}^{p}\Lambda_{ij}+\tau_j\Big)\beta_{yj}. \quad (3.28)$$

We shall show that if $R_0 > 1$ then for the above set of equations (3.22)–(3.28) the disease-free equilibrium is locally unstable. Then using the definition of the local asymptotical stability (Jordan & Smith, 1987) and writing $\boldsymbol{\xi} = (\pi_{x_1 1}, \pi_{h_1 1}, \pi_{h_2 1}, \pi_{y1}, \pi_{x_1 2}, \pi_{h_1 2}, \pi_{h_2 2}, \ldots, \pi_{yp}, \beta_{h_1 1}, \beta_{h_2 1}, \beta_{y1}, \beta_{h_1 2}, \beta_{h_2 2}, \beta_{y2}, \ldots, \beta_{yq})$, we deduce that there exists $\epsilon > 0$ such that for all t_0 and $\delta > 0$ there exists some $\boldsymbol{\xi}(0)$ with $|\boldsymbol{\xi}(0)| < \delta$ and $|\boldsymbol{\xi}(t_1)| > \epsilon$ for some $t_1 \geq t_0$.

Hence returning to our earlier system of differential equations (3.14)-(3.21) when $R_0 > 1$ and writing $\boldsymbol{\eta} = (\pi_{x_1 1}, \pi_{h_1 1}, \pi_{h_2 1}, \pi_{y1}, \pi_{z1}, \pi_{x_1 2}, \pi_{h_1 2}, \pi_{h_2 2}, \ldots, \pi_{yp}, \pi_{zp}, \beta_{h_1 1}, \beta_{h_2 1}, \beta_{y_1}, \beta_{h_1 2}, \beta_{h_2 2}, \beta_{y2}, \ldots, \beta_{yq})$, we deduce that there exists $\epsilon > 0$ such that for all t_0 and $\delta > 0$ taking $\pi_{zi}(0) = 0$, $\boldsymbol{\eta}(0)$ with $|\boldsymbol{\eta}(0)| < \delta$ and $|\boldsymbol{\eta}(t_1)| \geq |\boldsymbol{\xi}(t_1)| > \epsilon$ for some $t_1 \geq t_0$ as in the earlier case. This is because $\boldsymbol{\xi}(t)$ behaves the same in both sets of equations. In other words local instability of the second set of linearised equations (3.22) - (3.28) for $R_0 > 1$ implies local instability of the first set.

Thus our new system will consider $4p + 3q$ equations. These $4p + 3q$ differential equations describe the neighbourhood of the equilibrium point and can be expressed in the form

$$\frac{d\boldsymbol{x}}{dt} = \mathbf{J}\boldsymbol{x} \tag{3.29}$$

where $\boldsymbol{x}^T = (\pi_{x_1 1}, \pi_{h_1 1}, \pi_{h_2 1}, \pi_{y1}, \pi_{x_1 2}, \pi_{h_1 2}, \pi_{h_2 2}, \ldots, \pi_{yp}, \beta_{h_1 1}, \beta_{h_2 1}, \beta_{y1}, \beta_{h_1 2}, \ldots, \beta_{yq})$. $\mathbf{J}$ the Jacobian matrix of this system at the disease-free equilibrium is given by:

$$\boldsymbol{J} = \begin{pmatrix} \boldsymbol{K} & \boldsymbol{L} \\ \boldsymbol{M} & \boldsymbol{N} \end{pmatrix},$$

where $\boldsymbol{K}$ is the $4p \times 4p$ matrix.

$$\boldsymbol{K} = \begin{pmatrix} \boldsymbol{K}_1 & 0 & 0 & \ldots & 0 \\ 0 & \boldsymbol{K}_1 & 0 & \ldots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \ldots & \boldsymbol{K}_1 \end{pmatrix},$$

$$\boldsymbol{K}_1 = \begin{pmatrix} -\mu & 0 & \sigma(1-\alpha) & 0 \\ 0 & -(\mu+\sigma) & 0 & 0 \\ 0 & 0 & -(\mu+\sigma) & 0 \\ 0 & \sigma & 0 & -\mu \end{pmatrix},$$

and

$$\boldsymbol{L} = \begin{pmatrix} \boldsymbol{L}_{11} & \boldsymbol{L}_{12} & \dots & \boldsymbol{L}_{1q} \\ \boldsymbol{L}_{21} & \boldsymbol{L}_{22} & \dots & \boldsymbol{L}_{2q} \\ \vdots & \vdots & \ddots & \vdots \\ \boldsymbol{L}_{p1} & \boldsymbol{L}_{p2} & \dots & \boldsymbol{L}_{pq} \end{pmatrix}.$$

Here for $i = 1, 2, \dots p$, $j = 1, 2, \dots q$,

$$\boldsymbol{L}_{ij} = \begin{pmatrix} 0 & 0 & 0 \\ (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_y \\ \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_y \\ 0 & 0 & 0 \end{pmatrix}.$$

$$\boldsymbol{M} = \begin{pmatrix} \boldsymbol{M}_{11} & \boldsymbol{M}_{12} & \dots & \boldsymbol{M}_{1p} \\ \boldsymbol{M}_{21} & \boldsymbol{M}_{22} & \dots & \boldsymbol{M}_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ \boldsymbol{M}_{q1} & \boldsymbol{M}_{q2} & \dots & \boldsymbol{M}_{qp} \end{pmatrix},$$

we have for $k = 1, 2, \dots q$ and $l = 1, 2, \dots p$:

$$\boldsymbol{M}_{kl} = \begin{pmatrix} 0 & \Lambda_{lk} & 0 & 0 \\ 0 & 0 & \Lambda_{lk} & 0 \\ 0 & 0 & 0 & \Lambda_{lk} \end{pmatrix}.$$

Also

$$\boldsymbol{N} = \begin{pmatrix} \boldsymbol{N}_{11} & 0 & \dots & 0 \\ 0 & \boldsymbol{N}_{22} & \dots & 0 \\ \vdots & & & \vdots \\ 0 & 0 & \dots & \boldsymbol{N}_{qq} \end{pmatrix}$$

where for $j = 1, 2, \dots q$:

$$-\boldsymbol{N}_{jj} = \begin{pmatrix} \sum_{i=1}^{p} \Lambda_{ij} + \tau_j & 0 & 0 \\ 0 & \sum_{i=1}^{p} \Lambda_{ij} + \tau_j & 0 \\ 0 & 0 & \sum_{i=1}^{p} \Lambda_{ij} + \tau_j \end{pmatrix}.$$

Clearly, $(-\mu)$ is a p times repeated eigenvalue of $\boldsymbol{J}$. The remaining eigenvalues are eigenvalues of the matrix $\hat{\boldsymbol{J}}$ where

$$\hat{\boldsymbol{J}} = \begin{pmatrix} \hat{\boldsymbol{K}} & \hat{\boldsymbol{L}} \\ \hat{\boldsymbol{M}} & \boldsymbol{N} \end{pmatrix}.$$

Here we have that:

$$\hat{\boldsymbol{K}} = \begin{pmatrix} \hat{\boldsymbol{K}}_1 & 0 & 0 & \dots & 0 \\ 0 & \hat{\boldsymbol{K}}_1 & 0 & \dots & 0 \\ 0 & 0 & \hat{\boldsymbol{K}}_1 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & \hat{\boldsymbol{K}}_1 \end{pmatrix},$$

where

$$\hat{\boldsymbol{K}}_1 = \begin{pmatrix} -(\mu + \sigma) & 0 & 0 \\ 0 & -(\mu + \sigma) & 0 \\ \sigma & 0 & -\mu \end{pmatrix},$$

and

$$\hat{\boldsymbol{L}} = \begin{pmatrix} \hat{\boldsymbol{L}}_{11} & \hat{\boldsymbol{L}}_{12} & \dots & \hat{\boldsymbol{L}}_{1q} \\ \hat{\boldsymbol{L}}_{21} & \hat{\boldsymbol{L}}_{22} & \dots & \hat{\boldsymbol{L}}_{2q} \\ \vdots & \vdots & \ddots & \vdots \\ \hat{\boldsymbol{L}}_{p1} & \hat{\boldsymbol{L}}_{p2} & \dots & \hat{\boldsymbol{L}}_{pq} \end{pmatrix},$$

where for $i = 1, 2, \dots p$ and $j = 1, 2, \dots q$:

$$\hat{\boldsymbol{L}}_{ij} = \begin{pmatrix} (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_y \\ \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_y \\ 0 & 0 & 0 \end{pmatrix},$$

$$\hat{\boldsymbol{M}} = \begin{pmatrix} \hat{\boldsymbol{M}}_{11} & \hat{\boldsymbol{M}}_{12} & \dots & \hat{\boldsymbol{M}}_{1p} \\ \hat{\boldsymbol{M}}_{21} & \hat{\boldsymbol{M}}_{22} & \dots & \hat{\boldsymbol{M}}_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ \hat{\boldsymbol{M}}_{q1} & \hat{\boldsymbol{M}}_{q2} & \dots & \hat{\boldsymbol{M}}_{qp} \end{pmatrix},$$

where for $k = 1, 2, \dots p$ and $l = 1, 2, \dots q$, we have that:

$$\hat{\boldsymbol{M}}_{kl} = \begin{pmatrix} \Lambda_{lk} & 0 & 0 \\ 0 & \Lambda_{lk} & 0 \\ 0 & 0 & \Lambda_{lk} \end{pmatrix}.$$

We wish to look at the neighbourhood stability of the matrix $\boldsymbol{J}$ which is characterized by its eigenvalues. It is sufficient to consider the neighbourhood stability of the matrix $\hat{\boldsymbol{J}}$. We will have shown that the disease-free equilibrium is unstable if we find that at least one eigenvalue has a strictly positive real part. Recall our assumption (3.8), which states that for each pair of groups i and k of addicts, $\lambda_i > 0$,

$\lambda_k > 0$ and there exists a shooting gallery j_0 with:

$$P_{ij_0}(1 - \phi_{ij_0})\Lambda_{kj_0} > 0.$$

Let us call it assumption (A1).

Assumption (A1):

We assumed that $\lambda_i > 0 \ \forall \ i$ and, for each $k \neq i$, there exists a shooting gallery j_0 such that:

$$P_{ij_0}(1 - \phi_{ij_0})\Lambda_{kj_0} > 0.$$

In other words, assumption (A1) implies that any pair of groups of addicts can spread the disease from one to another. We make the additional assumption (A2) which states:

Assumption (A2):

(i) For each shooting gallery j there exists a group of addicts i with:

$$P_{ij} > 0.$$

In other words each shooting gallery can catch the disease from at least one group of addicts.

(ii) For each shooting gallery j there exists a group of addicts k with:

$$P_{kj}(1 - \phi_{kj}) > 0.$$

In other words each shooting gallery can spread the disease to at least one group of addicts.

Note that if M is sufficiently large the matrix $\hat{\boldsymbol{J}} + M\boldsymbol{I}$ is an M-matrix (i.e. all off-diagonal elements are non-negative). Then we have the following lemma:

Lemma 3.2.2. *Under assumptions (A1) and (A2) if M is sufficiently large to ensure that all diagonal elements of the matrix* $\hat{\boldsymbol{J}} + M\boldsymbol{I}$ *are strictly positive then matrix* $\hat{\boldsymbol{J}} + M\boldsymbol{I}$ *is irreducible.*

Proof. Assumption (A1) means that any group of addicts is reachable from any other, then assumption (A2) means that any shooting gallery is reachable from any group of addicts and from that shooting gallery the disease can spread back to the groups of addicts. So the matrix $\hat{\boldsymbol{J}} + M\boldsymbol{I}$ is irreducible. □

So we find that the matrix defined as $\hat{\boldsymbol{J}} + M\boldsymbol{I}$ is a positive irreducible matrix for M large enough, thus $\hat{\boldsymbol{J}} + M\boldsymbol{I}$ has a largest positive eigenvalue $(\omega_0 + M)$. This eigenvalue is real and positive. The right eigenvector $\boldsymbol{e}_0$ corresponding to $(\omega_0 + M)$ is a strictly positive eigenvector. From the definition of the eigenvalues and the eigenvector we deduce that:

$$\hat{\boldsymbol{J}}\boldsymbol{e}_0 \;=\; \omega_0\, \boldsymbol{e}_0, \qquad\qquad \text{where} \quad \boldsymbol{e}_0 \neq \boldsymbol{0}.$$

Consider the set of differential equations for $\boldsymbol{x}$ given by the system (3.15) - (3.21) with initial conditions given by $\boldsymbol{e}_0$ the solution is:

$$\boldsymbol{x} = \boldsymbol{e}_0\, e^{\omega_0 t},$$

where

$$\begin{aligned}\boldsymbol{x} &= \Big(\pi_{h_1 1}(t), \pi_{h_2 1}(t), \pi_{y1}(t), \pi_{h_1 2}(t), \pi_{h_2 2}(t), \pi_{y2}(t), \ldots, \pi_{h_1 p}(t), \pi_{h_2 p}(t), \pi_{yp}(t), \\ &\qquad \beta_{h_1 1}(t), \beta_{h_2 1}(t), \beta_{y1}(t), \beta_{h_1 2}(t), \beta_{h_2 2}(t), \beta_{y2}(t), \ldots, \beta_{h_1 q}(t), \beta_{h_2 q}(t), \beta_{yq}(t)\Big).\end{aligned}$$

It is more convenient and notionally simple to rewrite $\boldsymbol{x} = \boldsymbol{e}_0\ e^{\omega_0 t}$ in the following form:

$$\begin{aligned}\pi_{h_1 1}(t) &= \pi^0_{h_1 1} e^{\omega_0 t}, \\ \pi_{h_2 1}(t) &= \pi^0_{h_2 1} e^{\omega_0 t}, \\ &\vdots \\ \beta_{h_1 q}(t) &= \beta^0_{h_1 q} e^{\omega_0 t}, \\ \beta_{h_2 q}(t) &= \beta^0_{h_2 q} e^{\omega_0 t} \\ \beta_{yq}(t) &= \beta^0_{yq} e^{\omega_0 t}.\end{aligned}$$

By substituting these quantities into the equation (3.19), we deduce that for each j:

$$\begin{aligned}\frac{d}{dt}\beta_{h_1 j}(t) &= \frac{d}{dt}(\beta^0_{h_1 j}\ \ e^{\omega_0 t}), \\ &= \omega_0\ \beta^0_{h_1 j} e^{\omega_0 t}, \\ &= \left[\sum_{i=1}^{p} \Lambda_{ij}\pi^0_{h_1 i} - \left[\Big(\sum_{l=1}^{p} \Lambda_{lj}\Big) + \tau_j\right]\beta^0_{h_1 j}\right] e^{\omega_0 t}.\end{aligned}$$

It is straightforward to show the following by using a similar argument:

$$\begin{aligned}
\frac{d}{dt}\beta_{h_2j}(t) &= \omega_0\ \beta^0_{h_2j}e^{\omega_0 t}, \\
&= \left[\sum_{i=1}^{p}\Lambda_{ij}\pi^0_{h_2i} - \beta^0_{h_2j}\Big(\sum_{l=1}^{p}\Lambda_{lj}\Big) + \tau_j\right]e^{\omega_0 t}, \\
\frac{d}{dt}\beta_{yj}(t) &= \omega_0\ \beta^0_{yj}e^{\omega_0 t}, \\
&= \left[\sum_{i=1}^{p}\Lambda_{ij}\pi^0_{yi} - \left[\Big(\sum_{l=1}^{p}\Lambda_{lj}\Big) + \tau_j\right]\beta^0_{yj}\right]e^{\omega_0 t}.
\end{aligned}$$

Hence, we deduce that:

$$\begin{aligned}
\omega_0 &> -\left(\Big(\sum_{l=1}^{p}\Lambda_{lj}\Big) + \tau_j\right), \\
\beta^0_{h_1j} &= \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^0_{h_1i}}{(\sum_{l=1}^{p}\Lambda_{lj}) + \tau_j + \omega_0}, \\
\beta^0_{h_2j} &= \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^0_{h_2i}}{(\sum_{l=1}^{p}\Lambda_{lj}) + \tau_j + \omega_0}, \\
\text{and} \qquad \beta^0_{yj} &= \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^0_{yi}}{(\sum_{l=1}^{p}\Lambda_{lj}) + \tau_j + \omega_0}.
\end{aligned}$$

We use a similar argument with the system equations of the group i of injecting drug users. This gives us:

$$\begin{aligned}
\frac{d}{dt}\pi_{h_1i}(t) &= \frac{d}{dt}(\pi^0_{h_1i}\ \ e^{\omega_0 t}), \\
&= \omega_0\ \pi^0_{h_1i}\ e^{\omega_0 t}, \\
&= \left[(1-\delta)\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^0_{h_1j} + \beta^0_{h_2j}) + \alpha_y\beta^0_{yj}\big) - (\mu+\sigma)\pi^0_{h_1i}\right]e^{\omega_0 t},
\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}\pi_{h_2i}(t) &= \frac{d}{dt}(\pi^0_{h_2i}\ e^{\omega_0 t}),\\ &= \omega_0\ \pi^0_{h_2i}\ e^{\omega_0 t},\\ &= \left[\delta\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^0_{h_1j}+\beta^0_{h_2j})+\alpha_y\beta^0_{yj}\big)-(\mu+\sigma)\pi^0_{h_2i}\right]e^{\omega_0 t}.\end{aligned}$$

Hence,

$$\pi^0_{h_1i}\ (\mu+\sigma+\omega_0) = (1-\delta)\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^0_{h_1j}+\beta^0_{h_2j})+\alpha_y\beta^0_{yj}\big),$$

dividing the two sides by $(1-\delta)$ gives us:

$$\frac{\pi^0_{h_1i}}{1-\delta}\ (\mu+\sigma+\omega_0) = \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^0_{h_1j}+\beta^0_{h_2j})+\alpha_y\beta^0_{yj}\big). \tag{3.30}$$

Following a similar method, we deduce that:

$$\frac{\pi^0_{h_2i}}{\delta}\ (\mu+\sigma+\omega_0) = \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^0_{h_1j}+\beta^0_{h_2j})+\alpha_y\beta^0_{yj}\big). \tag{3.31}$$

Clearly the right hand sides of both equations (3.30) and (3.31) are equal. This implies that:

$$\frac{\pi^0_{h_1i}}{1-\delta}\ (\mu+\sigma+\omega_0) = \frac{\pi^0_{h_2i}}{\delta}\ (\mu+\sigma+\omega_0). \tag{3.32}$$

From equation (3.30) it also follows that $\omega_0+\mu+\sigma\neq 0$. Hence dividing both sides of (3.32) by $(\mu+\sigma+\omega_0)$ we will obtain that:

$$\frac{\pi^0_{h_1i}}{1-\delta} = \frac{\pi^0_{h_2i}}{\delta}.$$

Suppose that $\pi^0_{hi} = \pi^0_{h_1i}+\pi^0_{h_2i}$. We substitute the obtained relationship between

$\pi^0_{h_1 i}$ and $\pi^0_{h_2 i}$ to deduce that:

$$\begin{aligned}
\pi^0_{hi} &= \pi^0_{h_1 i} + \pi^0_{h_2 i}, \\
&= \pi^0_{h_1 i}\Big(1 + \frac{\delta}{1-\delta}\Big), \\
&= \frac{\pi^0_{h_1 i}}{1-\delta}.
\end{aligned}$$

Then, we can write $\pi^0_{h_1 i}$ and $\pi^0_{h_2 i}$ in terms of π^0_{hi}.

$$\begin{aligned}
\pi^0_{h_1 i} &= (1-\delta)\pi^0_{hi}, \\
\pi^0_{h_2 i} &= \delta \pi^0_{hi}.
\end{aligned}$$

Now, we express π^0_{hi} by adding the second and the third equations of the system of differential equations, hence we have:

$$\frac{d\pi_{hi}}{dt} = \sum_{j=1}^{q} \lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j} + \beta_{h_2 j}) + \alpha_y \beta_{yj}\big) - (\mu+\sigma)\pi_{hi}. \tag{3.33}$$

In the next step we substitute equation $\boldsymbol{x} = \boldsymbol{e}_0\, e^{\omega_0 t}$ into the equation (3.33), this will give:

$$\omega_0 \pi^0_{hi}\, e^{\omega_0 t} = \Big[\sum_{j=1}^{q} \lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^0_{h_1 j} + \beta^0_{h_2 j}) + \alpha_y \beta^0_{yj}\big) - (\mu+\sigma)\pi^0_{hi}\Big] e^{\omega_0 t}.$$

For the equation of π_{yi}, we follow a similar steps as earlier and we obtain the following:

$$\omega_0\ \pi^0_{yi} e^{\omega_0 t} = \Big[\sigma \pi^0_{h_1 i} - \mu \pi^0_{yi}\Big] e^{\omega_0 t}.$$

Hence $\omega_0 > -\mu$ and

$$\begin{aligned}\pi^0_{yi} &= \frac{\sigma\pi^0_{h_1 i}}{\omega_0+\mu},\\ &= \frac{\sigma(1-\delta)\pi^0_{hi}}{\omega_0+\mu}.\end{aligned}$$

Now we are in position to use the obtained results and relationship to express $\mathbf{Q}^*$ in terms of vector $\boldsymbol{x}$ elements. Recall that $\pi^0_{hi} = \pi^0_{h_1 i} + \pi^0_{h_2 i}$ and using earlier results we find that:

$$\begin{aligned}\pi^0_{hi}(\mu+\sigma+\omega_0) &= \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta^0_{h_1 j}+\beta^0_{h_2 j})+\alpha_y\beta^0_{yj}\big),\\ &= \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\sum_{k=1}^{p}\Lambda_{kj}(\alpha_h(\pi^0_{h_1 k}+\pi^0_{h_2 k})+\alpha_y\pi^0_{yk})}{(\sum_{l=1}^{p}\Lambda_{lj})+\tau_j+\omega_0}\right),\\ &= \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\sum_{k=1}^{p}\Lambda_{kj}\big(\alpha_h+\alpha_y\frac{\sigma(1-\delta)}{\mu+\omega_0}\big)\pi^0_{hk}}{(\sum_{l=1}^{p}\Lambda_{lj})+\tau_j+\omega_0}\right).\end{aligned}$$

Since $\mathbf{Q}^*$ is an irreducible positive $p \times p$ matrix, from the Perron-Frobenius Theorem, the spectral radius $\rho(\mathbf{Q}^*)$ is a positive real number and an eigenvalue of the matrix $\mathbf{Q}^*$, called the Perron-Frobenius eigenvalue. Moreover, $\mathbf{Q}^*$ has a left eigenvector $\boldsymbol{e} = (e_1, e_2, \ldots, e_p)$ with the eigenvalue $\rho(\mathbf{Q}^*)$ whose components are all positive. Recall that we proved that the spectral radius of $\mathbf{Q}^*$ is the basic reproductive number R_0. Thus,

$$\begin{aligned}\rho(\mathbf{Q}^*) &= R_0,\\ \boldsymbol{e}\cdot\mathbf{Q}^* &= R_0\boldsymbol{e}.\end{aligned}$$

Now,

$$\sum_{i=1}^{p} e_i \pi_{hi}^0 = f(\omega_0),$$

where

$$f(\omega_0) = \sum_{i=1}^{p} e_i \, \frac{\sum_{j=1}^{q} \lambda_i P_{ij}(1-\phi_{ij}) \sum_{k=1}^{p} \Lambda_{kj}\big(\alpha_h + \alpha_y \frac{\sigma(1-\delta)}{\mu+\omega_0}\big)\pi_{hk}^0}{(\mu+\sigma+\omega_0)[(\sum_{l=1}^{p}\Lambda_{lj}) + \tau_j + \omega_0]}.$$

Note that we have earlier shown that $\omega_0 > -\mu$ and:

$$\omega_0 > -\bigg((\sum_{l=1}^{p} \Lambda_{lj}) + \tau_j \bigg).$$

Hence

$$\omega_0 > -\bigg[\min \bigg(\mu, \min_{1 \leqslant j \leqslant q} \bigg((\sum_{l=1}^{p} \Lambda_{lj}) + \tau_j \bigg) \bigg) \bigg].$$

In this region $f(\omega_0)$ is a monotone decreasing function of ω_0 which approaches $+\infty$ as ω_0 tends to

$$-\bigg[\min \bigg(\mu, \min_{1 \leqslant j \leqslant q} (\sum_{l=1}^{p} \Lambda_{lj}) + \tau_j \bigg) \bigg],$$

from above. Moreover, $f(\omega) \longrightarrow 0$ as $\omega \longrightarrow \infty$. Hence $f(x)$ is monotone decreasing in

$$x > -\bigg[\min \bigg(\mu, \min_{1 \leqslant j \leqslant q} (\sum_{l=1}^{p} \Lambda_{lj}) + \tau_j \bigg) \bigg],$$

so the equation:

$$f(x) = \sum_{i=1}^{p} e_i \pi_{h_i}^0,$$

has a unique real root in

$$x > -\left[\min\left(\mu, \min_{1\leqslant j\leqslant q}\left(\sum_{l=1}^{p}\Lambda_{lj}\right)+\tau_j\right)\right].$$

But note that

$$\begin{aligned}
f(0) &= \frac{1}{\mu+\sigma}\sum_{i=1}^{p} e_i \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\sum_{k=1}^{p}\Lambda_{kj}(\alpha_h+\alpha_y\frac{\sigma(1-\delta)}{\mu})}{(\sum_{l=1}^{p}\Lambda_{lj})+\tau_j}\right)\pi^0_{h_k},\\
&= \sum_{i=1}^{p}\sum_{k=1}^{p} e_i Q^*_{ik}\pi^0_{h_k},\\
&= \boldsymbol{e}.\boldsymbol{Q}^*.{\boldsymbol{\pi_h}}^0,\\
&= R_0.\boldsymbol{e}.\boldsymbol{\pi}^0_h,\\
&> \boldsymbol{e}.\boldsymbol{\pi}^0_h.
\end{aligned}$$

Hence the unique root ω_0 of

$$f(x) = \sum_{i=1}^{p} e_i\pi^0_{h_i},$$

is strictly positive. As the eigenvalue ω_0 of $\hat{\boldsymbol{J}}$ (and hence also of $\boldsymbol{J}$) is real and strictly positive, we deduce that the disease-free equilibrium is unstable if $R_0 > 1$. □

Next, we turn our attention to the persistence of HCV. We shall show that if $R_0 > 1$ and HCV is initially present in the population either in the addicts groups or in shooting galleries, then the disease ultimately persists in both addicts and needles.

3.3 Persistence of the Disease

As we mentioned earlier R_0 determines the progress and spread of HCV. In this section we will prove that if $R_0 > 1$ and HCV is initially present in the population, either

in the addicts' groups or in shooting galleries, then the disease will be ultimately persistent in both addicts' groups and shooting galleries. In order to prove this, as in the proof of Theorem 3.1.4, we need to show in the following results that our system of ordinary differential equations (2.3) - (2.9), whose right hand side involves many unknown variables, can be replaced it with a differential inequality involving only one variable. Thus, we define $\pi_{h_1 i,\infty} = \liminf_{t \longrightarrow \infty} \pi_{h_1 i}(t)$, with similar definitions for the other model variables.

Lemma 3.3.1. *If* $\pi_{yi,\infty} = \liminf_{t \longrightarrow \infty} \pi_{yi}(t)$ *then,*

$$\pi_{yi,\infty} \geq \frac{\sigma}{\mu} \pi_{h_1 i,\infty}.$$

Proof. From equation (2.5), we have:

$$\begin{aligned} \frac{d}{dt}\Big[\pi_{yi} \exp(\mu t)\Big] &= \sigma \pi_{h_1 i} \exp(\mu t), \\ &\geq (\pi_{h_1 i,\infty} - \epsilon)\, \sigma \exp(\mu t), \qquad \forall \;\; t \geq t_{1i}(\epsilon), \end{aligned}$$

where $\pi_{h_1 i} \geq \pi_{h_1 i,\infty} - \epsilon$, for $t \geq t_{1i}(\epsilon)$. Integrating over $[t_{1i}(\epsilon), t]$ gives us,

$$\begin{aligned} \pi_{yi}(t) &\geq \pi_{yi}(t_{1i}(\epsilon)) \exp\Big[(-\mu)(t - t_{1i}(\epsilon))\Big] + (\pi_{h_1 i,\infty} - \epsilon)\sigma \left[\frac{1 - \exp\Big((-\mu)(t - t_{1i}(\epsilon))\Big)}{\mu}\right], \\ &\geq \sigma\Big(\frac{\pi_{h_1 i,\infty} - \epsilon}{\mu}\Big) - \epsilon, \qquad \forall \;\; t \geq t_{2i}(\epsilon), \end{aligned}$$

for some $t_{2i}(\epsilon)$, sufficiently large. Taking the lim inf and letting t go to infinity, we deduce that:

$$\pi_{yi,\infty} \geq \frac{\sigma}{\mu} \pi_{h_1 i,\infty} - \epsilon_1,$$

for $t \geq t_{2i}(\epsilon)$, where $\epsilon_1 = \epsilon(\mu + \sigma)/\mu$. Let us assume that $(\sigma/\mu)\ \pi_{h_1 i,\infty} > \pi_{yi,\infty}$. As $\epsilon_1 > 0$ is arbitrary, then we can choose:

$$\epsilon_1 = \frac{1}{2}\left[\frac{\sigma}{\mu}\pi_{h_1 i,\infty} - \pi_{yi,\infty}\right],$$

to obtain a contradiction and the result follows. □

Lemma 3.3.2. *If* $\pi_{zi,\infty} = \liminf_{t\longrightarrow\infty} \pi_{zi}(t)$ *then,*

$$\pi_{zi,\infty} \geq \frac{\alpha\sigma}{\mu}\pi_{h_2 i,\infty}.$$

Proof. Similar to the proof of Lemma 3.3.1 using equation (2.6). □

Corollary 3.3.3. *For* $j = 1, 2, \ldots q$, *if* $\beta_{h_1 j,\infty} = \liminf_{t\longrightarrow\infty} \beta_{h_1 j}(t)$ *then,*

$$\beta_{h_1 j,\infty} \geq \frac{\sum_{i=1}^{p} \Lambda_{ij}\pi_{h_1 i,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}.$$

Proof. We shall prove this using equation (2.7). Recall that $\pi_{h_1 i} \geq \pi_{h_1 i,\infty} - \epsilon_1$, for $t \geq t_{1i}(\epsilon),\ i = 1, 2, \ldots p$. Define:

$$t_1(\epsilon) = \max_{1\leq i\leq p}\{t_{1i}(\epsilon)\}.$$

Then for $t \geq t_1(\epsilon)$, we deduce that:

$$\begin{aligned}
\frac{d}{dt}\Big[\beta_{h_1 j}\exp\Big(\sum_{i=1}^{p}\Lambda_{ij} + \tau_j\Big)t\Big] &= \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_1 i}\exp\Big[\Big(\sum_{i=1}^{p}\Lambda_{ij} + \tau_j\Big)t\Big], \\
&\geq \sum_{i=1}^{p}\Lambda_{ij}(\pi_{h_1 i,\infty} - \epsilon)\exp\Big[\Big(\sum_{i=1}^{p}\Lambda_{ij} + \tau_j\Big)t\Big].
\end{aligned}$$

As we did above, integrating over $[t_1(\epsilon), t]$ gives:

$$\begin{aligned}
\beta_{h_1 j}(t) &\geq \beta_{h_1 j}(t_1(\epsilon)) \exp\Big[-\Big(\sum_{i=1}^{p} \Lambda_{ij} + \tau_j\Big)(t - t_1(\epsilon)) \\
&\quad + \sum_{i=1}^{p} \Lambda_{ij}(\pi_{h_1 i,\infty} - \epsilon) \left[\frac{1 - \exp\Big[-\Big(\sum_{i=1}^{p} \Lambda_{ij} + \tau_j\Big)(t - t_1(\epsilon))\Big]}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j} \right], \\
&\geq \frac{\sum_{i=1}^{p} \Lambda_{ij}(\pi_{h_1 i,\infty} - \epsilon)}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j} - \epsilon,
\end{aligned}$$

for $t \geq t_2(\epsilon)$, some $t_2(\epsilon) > 0$. Taking the lim inf and letting t go to infinity, we deduce that:

$$\beta_{h_1 j,\infty} \geq \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi_{h_1 i,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j} - \epsilon_2,$$

where ϵ_2 is positive and

$$\epsilon_2 = \epsilon \left(\frac{\sum_{i=1}^{p} \Lambda_{ij}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j} + 1 \right).$$

Suppose that

$$\frac{\sum_{i=1}^{p} \Lambda_{ij} \pi_{h_1 i,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j} > \beta_{h_1 j,\infty}.$$

Since ϵ_2 is positive and arbitrary, then we can choose it as:

$$\epsilon_2 = \frac{1}{2} \left(\frac{\sum_{i=1}^{p} \Lambda_{ij} \pi_{h_1 i,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j} - \beta_{h_1 j,\infty} \right),$$

which leads us to a contradiction. Thus,

$$\beta_{h_1 j,\infty} \geq \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi_{h_1 i,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}.$$

□

We use a similar argument with equations (2.8) and (2.9), to obtain the following for $j = 1, 2, \ldots q$:

$$\beta_{h_2 j,\infty} \geq \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi_{h_2 i,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}, \tag{3.34}$$

and

$$\beta_{yj,\infty} \geq \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi_{yi,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}. \tag{3.35}$$

Next, we attempt to determine the relationship between $\pi_{h_1 i,\infty}$ and $\pi_{h_2 i,\infty}$. The following lemma discusses finding this relationship.

Lemma 3.3.4.

$$(1-\delta)\pi_{h_2 i,\infty} = \delta \pi_{h_1 i,\infty}.$$

Proof. We follow a similar proof to Corson et al. (2012). Assume that $(1-\delta)\pi_{h_2 i,\infty} \neq \delta \pi_{h_1 i,\infty}$. Hence, either $(1-\delta)\pi_{h_2 i,\infty} > \delta \pi_{h_1 i,\infty}$ or $(1-\delta)\pi_{h_2 i,\infty} < \delta \pi_{h_1 i,\infty}$. Suppose that $(1-\delta)\pi_{h_2 i,\infty} > \delta \pi_{h_1 i,\infty}$. From equations (2.3) and (2.4), and considering:

$$\frac{d}{dt}\left(\frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}\right),$$

we find that $\delta \pi_{h_1 i} - (1-\delta)\pi_{h_2 i} \longrightarrow 0$ as $t \longrightarrow \infty$. So given $\epsilon > 0$ there exists $t_1(\epsilon) > 0$ such that $\delta \pi_{h_1 i} > (1-\delta)\pi_{h_2 i} - (\epsilon/2)$ for $t \geq t_1(\epsilon)$. Moreover there exists $t_2(\epsilon) > t_1(\epsilon)$

such that:

$$\begin{aligned}\delta\pi_{h_1 i} \geq (1-\delta)\pi_{h_2 i} - \frac{\epsilon}{2} &\geq (1-\delta)\left(\pi_{h_2 i,\infty} - \frac{\epsilon}{2(1-\delta)}\right) - \frac{\epsilon}{2}, \\ &= (1-\delta)\pi_{h_2 i,\infty} - \epsilon,\end{aligned}$$

for $t \geq t_2(\epsilon)$. Taking the lim inf we deduce that:

$$\delta\pi_{h_1 i,\infty} \geq (1-\delta)\pi_{h_2 i,\infty} - \epsilon.$$

As ϵ is positive and arbitrary we deduce that:

$$\delta\pi_{h_1 i,\infty} \geq (1-\delta)\pi_{h_2 i,\infty}. \tag{3.36}$$

Assuming that $(1-\delta)\pi_{h_2 i,\infty} < \delta\pi_{h_1 i,\infty}$, and using a similar argument we deduce that:

$$(1-\delta)\pi_{h_2 i,\infty} \geq \delta\pi_{h_1 i,\infty}. \tag{3.37}$$

From inequalities (3.36) and (3.37), the result follows and we obtain that:

$$(1-\delta)\pi_{h_2 i,\infty} = \delta\pi_{h_1 i,\infty}.$$

□

Lemma 3.3.5. *Provided that at least one of* $\pi_{h_1 i_0}(0)$, $\pi_{h_2 i_0}(0)$, $\pi_{y i_0}(0)$, $\beta_{h_1 j_0}(0)$, $\beta_{h_2 j_0}(0)$ *and* $\beta_{y j_0}(0) > 0$ *for some* $i_0 = 1, 2, \ldots p$ *or* $j_0 = 1, 2, \ldots q$, *then for all* $i = 1, 2, \ldots p$ *and* $j = 1, 2, \ldots q$, $\pi_{h_1 i}(\Delta t)$, $\pi_{h_2 i}(\Delta t)$, $\pi_{y i}(\Delta t)$, $\beta_{h_1 j}(\Delta t)$, $\beta_{h_2 j}(\Delta t)$ *and* $\beta_{y j}(\Delta t)$ *are all strictly greater than zero for small* $\Delta t > 0$.

Proof. We define $\pi_i = \sum_\xi \pi_{\xi i}$, $\beta_j = \sum_\xi \beta_{\xi j}$ for $i = 1, 2, \ldots p$, $j = 1, 2, \ldots q$ and $\xi = h_1, h_2, y$ and $\pi_i^\dagger = \sum_\eta \pi_{\eta i}$ for $\eta = h_1, h_2, y, z$. Also, define $\psi_i = 1 - \pi_i^\dagger$.

Suppose first that $\pi_{i_0}(0) > 0$ for some $i_0 = 1, 2, \ldots p$. Then for any addict group k by Assumption A1, there exists j_0 with

$$P_{kj_0}(1 - \phi_{kj_0})\Lambda_{i_0 j_0} > 0. \tag{3.38}$$

Then

$$\beta_{j_0}(t) = \beta_{h_1 j_0}(t) + \beta_{h_2 j_0}(t) + \beta_{y j_0}(t),$$

and using a Taylor series expansion about $t = 0$ and appropriate model equations we have, for $\Delta t > 0$:

$$\beta_{j_0}(\Delta t) = \beta_{j_0}(0) + \left(\sum_{i=1}^{p} \Lambda_{ij_0}\pi_i(0) - \Big[\Big(\sum_{i=1}^{p} \Lambda_{ij_0} \Big) + \tau_{j_0} \Big] \beta_{j_0}(0) \right) \Delta t + o(\Delta t),$$

so, if $\beta_{j_0}(0) = 0$ then:

$$\beta_{j_0}(\Delta t) \geq \Lambda_{i_0 j_0}\pi_{i_0}(0)\Delta t + o(\Delta t) > 0,$$

if Δt is small enough, as $\Lambda_{i_0 j_0}\pi_{i_0}(0) > 0$. Thus, we choose $\Delta t > 0$ small enough and starting at time $t = \Delta t$ rather than $t = 0$ we can assume that $\beta_{j_0}(0) > 0$. Now, for addict group k, if $\psi_k(0) = 0$, then as:

$$\begin{aligned} \frac{d\psi_k}{dt} &= \frac{d\pi_{x_1 k}}{dt} + \frac{d\pi_{xk}}{dt}, \\ &= -\lambda_k \psi_k \sum_{j=1}^{q} P_{kj}(1 - \phi_{kj})A_j + \mu(1 - \psi_k) + \sigma(1 - \alpha)\pi_{h_2 k}, \end{aligned}$$

where $A_j = \alpha_h(\beta_{h_1 j} + \beta_{h_2 j}) + \alpha_y \beta_{yj}$, we have:

$$\begin{aligned}\psi_k(\Delta t) &= \psi_k(0) - \lambda_k \psi_k(0)\Delta t \sum_{j=1}^{q} P_{kj}(1-\phi_{kj})A_j(0) + \mu(1-\psi_k(0))\Delta t \\ &\quad + \sigma(1-\alpha)\pi_{h_2 k}(0)\Delta t + o(\Delta t).\end{aligned}$$

Then:

$$\psi_k(\Delta t) \geq \mu \Delta t + o(\Delta t),$$

if Δt is small enough. By choosing $\Delta t > 0$ small enough and starting at time $t = \Delta t$ rather than $t = 0$, we can assume that:

$$\psi_k(0) > 0,$$

and

$$\beta_{j_0}(0) > 0.$$

We have

$$\begin{aligned}\pi_k(\Delta t) &= \pi_k(0) + \lambda_k \psi_k(0) \sum_{j=1}^{q} P_{kj}(1-\phi_{kj})A_j(0)\Delta t - \mu \pi_k(0)\Delta t \\ &\quad - \sigma \pi_{h_2 k}(0)\Delta t + o(\Delta t).\end{aligned}$$

In the case where $\pi_k(0) = 0$:

$$\pi_k(\Delta t) \geq \lambda_k \psi_k(0) P_{kj_0}(1-\phi_{kj_0}) \min[\alpha_h, \alpha_y]\beta_{j_0}(0)\Delta t + o(\Delta t).$$

By using (3.38), we can assume without loss of generality that:

$$\pi_k(0) > 0 \quad \text{and} \quad \psi_k(0) > 0.$$

Note that as k can be any addict group we can assume without loss of generality that $\pi_k(0) > 0$ and $\psi_k(0) > 0$ for $k = 1, 2, \ldots p$. Now for any shooting gallery say j, then by Assumption A2(i) there exists a group of addicts i_1 with

$$P_{i_1 j} > 0.$$

Then, we have:

$$\beta_j(\Delta t) = \beta_j(0) + \left(\sum_{i=1}^{p} \Lambda_{ij} \pi_i(0) - \Big[\sum_{i=1}^{p} \Lambda_{ij} + \tau_j \Big] \beta_j(0) \right) \Delta t + o(\Delta t).$$

Hence, if $\beta_j(0) = 0$ we deduce that:

$$\beta_j(\Delta t) \geq \Lambda_{i_1 j} \pi_{i_1}(0) \Delta t + o(\Delta t),$$

and from Assumption A2(i) we have:

$$\Lambda_{ij} = \frac{\lambda_{i_1} P_{i_1 j} n_{i_1}}{m_j} > 0.$$

If we start at $t = \Delta t$ instead of $t = 0$, we deduce that without loss of generality:

$$\pi_k(0) > 0, \quad \psi_k(0) > 0 \text{ and } \beta_j(0) > 0, \qquad \text{for} \quad k = 1, 2, \ldots p \quad \text{and} \quad j = 1, 2, \ldots q.$$

On the other hand, if for some k $\pi_{h_1k}(0) = 0$ we deduce that:

$$\begin{aligned}\pi_{h_1k}(\Delta t) &= \pi_{h_1k}(0) + (1-\delta)\lambda_k\psi_k(0)\sum_{j=1}^{q} P_{kj}(1-\phi_{kj})A_j(0)\Delta t \\ &\quad - (\mu+\sigma)\pi_{h_1k}(0)\Delta t + o(\Delta t), \\ &\geq (1-\delta)\lambda_k\psi_k(0)\min[\alpha_h,\alpha_y]\sum_{j=1}^{q} P_{kj}(1-\phi_{kj})\beta_j(0)\Delta t + o(\Delta t).\end{aligned}$$

From Assumption A1, we pick any group of addicts i and we deduce that there exists a shooting gallery j_1 with:

$$P_{kj_1}(1-\phi_{kj_1})\Lambda_{ij_1} > 0.$$

Hence $P_{kj_1}(1-\phi_{kj_1}) > 0$ and $\Lambda_{ij_1} > 0$ and moreover,

$$\begin{aligned}\pi_{h_1k}(\Delta t) &\geq (1-\delta)\lambda_k\psi_k(0)\min[\alpha_h,\alpha_y]P_{kj_1}(1-\phi_{kj_1})\beta_{j_1}(0)\Delta t + o(\Delta t), \\ &> 0,\end{aligned}$$

if Δt is small enough. Thus, without loss of generality $\pi_{h_1k}(0) > 0$. We use a similar argument with the other variables, we obtain that without loss of generality we may assume that $\pi_{h_2k}(0) > 0$, $\pi_{yk}(0) > 0$ and $\pi_{zk}(0) > 0$.

Now consider the case where $\beta_{h_1j}(0) = 0$ for some j. By Assumption A2(i), there exists a group of addicts i_1 with:

$$P_{i_1j} > 0.$$

Hence,

$$\begin{aligned}\beta_{h_1 j}(\Delta t) &= \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_1 i}(0)\Delta t + o(\Delta t),\\ &\geq \Lambda_{i_1 j}\pi_{h_1 i_1}(0)\Delta t + o(\Delta t),\\ &> 0,\end{aligned}$$

if Δt is small enough. So, without loss of generality we may assume the case where $\beta_{h_1 j}(0) > 0$. Following a similar argument we may assume that $\beta_{h_2 j}(0) > 0$ and $\beta_{yj}(0) > 0$. Hence the results of Lemma 3.3.5 follow in the case where $\pi_{i_0}(0) > 0$ for some $i_0 = 1, 2, \ldots p$.

Next suppose that $\beta_{yj_0}(0) > 0$ for some $j_0 = 1, 2, \ldots q$. Now, by Assumption A2(ii) there exists a group of addicts k_0 with:

$$P_{k_0 j_0}(1 - \phi_{k_0 j_0}) > 0.$$

Arguing as above and without loss of generality we may assume that $\pi_{k_0}(0) > 0$. Then the results follow by the previous case. This completes our proof of the lemma. □

Lemma 3.3.6. *Suppose that at least one of $\pi_{h_1 i_0,\infty}$, $\pi_{h_2 i_0,\infty}$, $\pi_{y i_0,\infty}$, $\beta_{h_1 j_0,\infty}$, $\beta_{h_2 j_0,\infty}$ and $\beta_{y j_0,\infty}$ is strictly greater than zero for some $i_0 = 1, 2, \ldots p$ or $j_0 = 1, 2, \ldots q$. Then for $i = 1, 2, \ldots p$ and $j = 1, 2, \ldots q$, $\pi_{h_1 i,\infty}$, $\pi_{h_2 i,\infty}$, $\pi_{yi,\infty}$, $\beta_{h_1 j,\infty}$, $\beta_{h_2 j,\infty}$ and $\beta_{yj,\infty}$ are all strictly greater than zero.*

Proof. Suppose first that $\pi_{h_1 i_0,\infty} > 0$ for some $i_0 = 1, 2, \ldots p$. Then by Lemmas 3.3.1, 3.3.2 and Lemma 3.3.4 we have $\pi_{y i_0,\infty} > 0$, $\pi_{z i_0,\infty} > 0$ and $\pi_{h_2 i_0,\infty} > 0$.

For any addict group k by Assumption A1 there exists a shooting gallery j_0 with:

$$P_{kj_0}(1-\phi_{kj_0})\Lambda_{i_0j_0} > 0.$$

Then by Corollary 3.3.3:

$$\begin{aligned}
\beta_{h_1j_0,\infty} &\geq \frac{\sum_{i=1}^{p}\Lambda_{ij_0}\pi_{h_1i,\infty}}{\sum_{i=1}^{p}\Lambda_{ij_0}+\tau_{j_0}}, \\
&\geq \frac{\Lambda_{i_0j_0}\pi_{h_1i,\infty}}{\sum_{i=1}^{p}\Lambda_{ij_0}+\tau_{j_0}}, \\
&> 0.
\end{aligned}$$

So there exists $t_0 > 0$ and $\epsilon_0 > 0$ such that for $t \geq t_0$, $\beta_{h_1j_0} \geq \epsilon_0 > 0$. Now

$$\begin{aligned}
\psi_k &= 1-\pi_{h_1k}-\pi_{h_2k}-\pi_{yk}-\pi_{zk}, \\
\frac{d\psi_k}{dt} &= -\lambda_k\psi_k\sum_{j=1}^{q}P_{kj}(1-\phi_{kj})A_j+\mu(1-\psi_k)+\sigma(1-\alpha)\pi_{h_2k}, \\
&\geq \mu-\psi_k\Big(\mu+\lambda_k\max(\alpha_h,\alpha_y)\Big), \\
&= \mu-C_k\psi_k, \qquad (3.39)
\end{aligned}$$

where

$$C_k = \Big(\mu+\lambda_k\max(\alpha_h,\alpha_y)\Big).$$

Hence,

$$\frac{d}{dt}(\psi_k\ e^{C_kt}) \geq \mu\ e^{C_kt}.$$

Integrating over $[t_0, t)$:

$$\begin{aligned}\psi_k(t)\ e^{C_k t} - \psi_k(t_0)e^{C_k t_0} &\geq \frac{\mu}{C_k}(e^{C_k t} - e^{C_k t_0}),\\ \psi_k(t) &\geq \psi_k(t_0)e^{-C_k(t-t_0)} + \frac{\mu}{C_k}\Big(1 - e^{-C_k(t-t_0)}\Big).\end{aligned}$$

Thus, there exists $t_1 > t_0$ such that for $t \geq t_1$, we have that:

$$\psi_k(t) \geq \frac{\mu}{2C_k} = \epsilon_1.$$

From equation (2.3) of our model:

$$\begin{aligned}\frac{d\pi_{h_1 k}}{dt} &= \sum_{j=1}^{q}(1-\delta)(1 - \pi_{h_1 k} - \pi_{h_2 k} - \pi_{yk} - \pi_{zk})\lambda_k P_{kj}(1-\phi_{kj})(\alpha_h(\beta_{h_1 j} + \beta_{h_2 j})\\ &\qquad + \alpha_y \beta_{yj}) - (\mu + \sigma)\pi_{h_1 k}.\end{aligned}$$

Then for $t \geq t_1$:

$$\frac{d\pi_{h_1 k}}{dt} \geq (1-\delta)\epsilon_0\epsilon_1\lambda_k P_{kj_0}(1-\phi_{kj_0})\alpha_h - (\mu+\sigma)\pi_{h_1 k}.$$

This has the same form as the equation (3.39). Thus, there exists $t_2 \geq t_1$ and $\epsilon_2 > 0$ such that for $t \geq t_2$:

$$\pi_{h_1 k} \geq \epsilon_2 > 0,$$

hence $\pi_{h_1 k,\infty} > 0$. By Lemmas 3.3.1, 3.3.2 and 3.3.4, we have $\pi_{yk,\infty} > 0$, $\pi_{zk,\infty} > 0$ and $\pi_{h_2 k,\infty} > 0$.

Now, for any shooting gallery j, by Assumption A2(i) there exists a group of

addicts i_1 with:

$$P_{i_1 j} > 0. \tag{3.40}$$

Then, by Corollary 3.3.3, we have:

$$\begin{aligned} \beta_{h_1 j,\infty} &\geq \frac{\sum_{i=1}^{p} \Lambda_{ij} \pi_{h_1 i,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}, \\ &\geq \frac{\Lambda_{i_1 j} \pi_{h_1 i_1,\infty}}{\sum_{i=1}^{p} \Lambda_{ij} + \tau_j}, \\ &> 0. \end{aligned}$$

On the other hand, we also know that $\pi_{h_2 i_1,\infty}$ and $\pi_{y i_1,\infty}$ are greater than zero, hence similar arguments with $\beta_{h_2 j}$ and β_{yj} show that $\beta_{h_2 j,\infty} > 0$ and $\beta_{yj,\infty} > 0$. Hence we have proved Lemma 3.3.6 in the case where $\pi_{h_1 i_0,\infty} > 0$ for some $i = 1, 2, \ldots p$. The case where $\pi_{h_2 i_0,\infty} > 0$ then follows from Lemma 3.3.4.

In the case where $\pi_{y i_0,\infty} > 0$ for some $i = 1, 2, \ldots p$, then for any addict group k by Assumption A1, there exists a shooting gallery j_0 with:

$$P_{k j_0}(1 - \phi_{k j_0}) \Lambda_{i_0 j_0} > 0.$$

Then, arguing as above, $\beta_{y j_0,\infty} > 0$ follows from the inequality (3.35). A similar argument to the one used in the case where $\pi_{h_1 i_0,\infty} > 0$ shows that $\pi_{h_1 k,\infty} > 0$. The result of Lemma 3.3.6 then follows in the case where $\pi_{y i_0,\infty} > 0$.

Next consider the case where $\beta_{h_1 j_1,\infty} > 0$ for some $j_1 \in \{1, 2, \ldots q\}$. Now, by

Assumption A2(ii), there exists a group of addicts k_1 with:

$$P_{k_1 j_1}(1 - \phi_{k_1 j_1}) > 0.$$

Arguing as above and without loss of generality we may assume that $\pi_{h_1 k_1,\infty} > 0$. Then the results follow as in the previous case. Finally, in the case where $\beta_{h_2 j_1,\infty} > 0$ or $\beta_{y j_1,\infty} > 0$ a straightforward following of a similar argument as for $\beta_{h_1 j_1,\infty} > 0$ shows that $\pi_{h_1 k_1,\infty} > 0$ and the result follows which completes the proof. □

Theorem 3.3.7. *Suppose that $R_0 > 1$ and either*

(i) for some $i_0 \in 1, 2, \ldots p$ at least one of

$$\pi_{h_1 i_0}(0), \quad \pi_{h_2 i_0}(0) \quad or \quad \pi_{y i_0}(0),$$

is strictly positive, or

(ii) for some $j_0 \in 1, 2, \ldots q$ at least one of

$$\beta_{h_1 j_0}(0), \quad \beta_{h_2 j_0}(0) \quad or \quad \beta_{y j_0}(0),$$

is strictly positive.

Then there exists $\eta > 0$ such that for $t \geq \eta$, $i = 1, 2, \ldots p, j = 1, 2, \ldots q$, $\pi_{h_1 i} \geq \epsilon \pi^*_{h_1 i}$, $\pi_{h_2 i} \geq \epsilon \pi^*_{h_2 i}$, $\pi_{y i} \geq \epsilon \pi^*_{y i}$, $\beta_{h_1 j} \geq \epsilon \beta^*_{h_1 j}$, $\beta_{h_2 j} \geq \epsilon \beta^*_{h_2 j}$ and $\beta_{y j} \geq \epsilon \beta^*_{y j}$, where ϵ is a fixed positive and small value depending only on the model parameters not the initial conditions.

Proof. By Lemma 3.3.6 we need to consider only two cases, the first case where for all $i = 1, 2, \ldots p$ and $j = 1, 2, \ldots q$,$\pi_{h_1 i,\infty}, \pi_{h_2 i,\infty}, \pi_{y i,\infty}, \beta_{h_1 j,\infty}, \beta_{h_2 j,\infty}$ and $\beta_{y j,\infty}$ all are

strictly positive (note i and j, not i_0 and j_0). The second case, where they all are zero (again i and j, not i_0 and j_0). The first case is fairly straightforward. The second is more complicated and probably needs more explanations. Thus let assume that:

Case 1:

For all $i = 1, 2, \ldots p, j = 1, 2, \ldots q$, $\pi_{h_1 i_0,\infty}$, $\pi_{h_2 i_0,\infty}$, $\pi_{y i_0,\infty}$, $\beta_{h_1 j_0,\infty}$, $\beta_{h_2 j_0,\infty}$ and $\beta_{y j_0,\infty}$ are all strictly greater than zero. There exists $\epsilon_1 > 0$ such that for $i = 1, 2, \ldots p, j = 1, 2, \ldots q$ $\pi_{h_1 i,\infty} \geq \frac{1}{2}\ \epsilon_1 \pi^*_{h_1 i}$, $\pi_{h_2 i,\infty} \geq \frac{1}{2}\ \epsilon_1 \pi^*_{h_2 i}$, $\pi_{y i,\infty} \geq \frac{1}{2}\ \epsilon_1 \pi^*_{y i}$, $\beta_{h_1 j,\infty} \geq \frac{1}{2}\ \epsilon_1 \beta^*_{h_1 j}$, $\beta_{h_2 j,\infty} \geq \frac{1}{2}\ \epsilon_1 \beta^*_{h_2 j}$ and $\beta_{y j,\infty} \geq \frac{1}{2}\ \epsilon_1 \beta^*_{y j}$. By the definition of $\pi_{h_1 i,\infty}$ and for $i = 1, 2, \ldots p$, there exists a time $T_{h_1 i}$ such that for $t \geq T_{h_1 i}$, then $\pi_{h_1 i}(t) \geq \frac{1}{4}\ \epsilon_1 \pi^*_{h_1 i}$. Similarly, there is a time $T_{h_2 i}$ such that for $t \geq T_{h_2 i}$, then $\pi_{h_2 i}(t) \geq \frac{1}{4}\ \epsilon_1 \pi^*_{h_2 i}$, $T_{y i}$ such that for $t \geq T_{y i}$, then $\pi_{y i}(t) \geq \frac{1}{4}\ \epsilon_1 \pi^*_{y i}$, $T_{z i}$ such that for $t \geq T_{z i}$, then $\pi_{z i}(t) \geq \frac{1}{4}\ \epsilon_1 \pi^*_{z i}$. Moreover, for $j = 1, 2, \ldots q$ there also exists a time $T_{\beta_{h_1 j}}$ such that for $t \geq T_{\beta_{h_1 j}}$, then $\beta_{h_1 j}(t) \geq \frac{1}{4}\ \epsilon_1 \beta^*_{h_1 j}$, $T_{\beta_{h_2 j}}$ such that for $t \geq T_{\beta_{h_2 j}}$, then $\beta_{h_2 j}(t) \geq \frac{1}{4}\ \epsilon_1 \beta^*_{h_2 j}$ and $T_{\beta_{y j}}$ such that for $t \geq T_{\beta_{y j}}$, then $\beta_{y j}(t) \geq \frac{1}{4}\ \epsilon \beta^*_{y j}$. Choose η to be the maximum time,

$$\eta = \max_{\substack{i=1,2,\ldots p \\ j=1,2,\ldots q}} \{T_{h_1 i}, T_{h_2 i}, T_{y i}, T_{z i}, T_{\beta_{h_1 j}}, T_{\beta_{h_2 j}}, T_{\beta_{y j}}\},$$

and define $\epsilon = \frac{1}{4}\epsilon_1$. Hence the theorem is true.

Case 2:

For $i = 1, 2, \ldots p$ and $j = 1, 2, \ldots q$, $\pi_{h_1 i_0,\infty} = \pi_{h_2 i_0,\infty} = \pi_{y i_0,\infty} = \beta_{h_1 j_0,\infty} = \beta_{h_2 j_0,\infty} = \beta_{y j_0,\infty} = 0$ are all zero. Let us suppose that $\epsilon > 0$, and pick $k_0 \in \{1, 2, \ldots p\}$. Lemma 3.3.5 shows that $\pi_{h_1 k_0}(\Delta t) > 0$. As $\pi_{h_1 k_0,\infty} = 0$ there exists $\xi \geq \Delta t$ where $\pi_{h_1 k_0}(\xi) < \frac{1}{2}\ \epsilon \pi^*_{h_1 k_0}$. Suppose that $\pi_{h_1 k_0}(t)$ goes beneath $\frac{1}{2}\ \epsilon \pi^*_{h_1 k_0}$ at time $t_{0 k_0}$, then

next rises above $\frac{1}{2}\,\epsilon\pi^*_{h_1k_0}$ at time t_{1k_0}. More precisely following Corson et al. (2012) we define $t_{0k_0} = \inf\{\xi \geq \Delta t, \pi_{h_1k_0}(\xi) < \frac{1}{2}\,\epsilon\pi^*_{h_1k_0}\}$ to be the first time after $t = \Delta t$ where $\pi_{h_1k_0}$ starts to go below $\frac{1}{2}\,\epsilon\pi^*_{h_1k_0}$ and $t_{1k_0} = \inf\{\xi \geq t_{0k_0}, \pi_{h_1k_0}(\xi) \geq \frac{1}{2}\,\epsilon\pi^*_{h_1k_0}\}$ to be the first time after $t = t_{0k_0}$ where $\pi_{h_1k_0}$ rises above $\frac{1}{2}\,\epsilon\pi^*_{h_1k_0}$. If $\pi_{h_1k_0}(\Delta t) \geq \frac{1}{2}\,\epsilon\pi^*_{h_1k_0}$, then by the definition of t_{0k_0} we have $\pi_{h_1k_0}(t_{0k_0} + \nu) < \frac{1}{2}\,\epsilon\pi^*_{h_1k_0}$ for some ν small and positive. Therefore, $t_{1k_0} > t_{0k_0}$ and by continuity $\pi_{h_1k_0}(t_{0k_0}) = \frac{1}{2}\,\epsilon\pi^*_{h_1k_0} = \pi_{h_1k_0}(t_{1k_0})$ and so $\pi_{h_1k_0} \leq \frac{1}{2}\,\epsilon\pi^*_{h_1k_0}$ in (t_{0k_0}, t_{1k_0}) and $\pi_{h_1k_0} > \frac{1}{2}\,\epsilon\pi^*_{h_1k_0}$ immediately after time t_{1k_0}. Define the following:

$$S_1(t) = \left\{ i \in 1, 2, \ldots p, \pi_{h_1i}(t) \geq \frac{1}{2}\,\epsilon\pi^*_{h_1i} \right\},$$

$$S_2(t) = \left\{ i \in 1, 2, \ldots p, \pi_{h_1i}(t) < \frac{1}{2}\,\epsilon\pi^*_{h_1i} \right\}.$$

Case 2a:

For Δt small and positive.

$$S_1(t_{0k_0} + \Delta t) = \emptyset.$$

This implies that all $\pi_{h_1i}(t_{0k_0} + \Delta t) < \frac{1}{2}\,\epsilon\pi^*_{h_1i}$ at time $t_{0k_0} + \Delta t$. Similarly to t_{1k_0} we define $t_{1k_02a} \leq t_{1k_0}$ to be the first time after $t = t_{0k_0}$ where some π_{h_1i} rises above $\frac{1}{2}\,\epsilon\pi^*_{h_1i}$ and $t_{1k_02a} = \inf\{\xi \geq t_{0k_0}, \pi_{h_1i}(\xi) \geq \frac{1}{2}\,\epsilon\pi^*_{h_1i}$ for some $i \in 1, 2, \ldots p\}$. Thus for $t \in (t_{0k_0}, t_{1k_02a})$ we are still in Case 2a. To discuss this case we need the following lemmas:

Lemma 3.3.8. *If $\Delta > 0$ is small and positive then for each $i \in \{1, 2, \ldots p\}$ there exists a time $\overline{T}_{1k_0i} > 0$ such that if $t_{0k_0} + \overline{T}_{1k_0i} < t_{1k_0}$, then for all $t \in [t_{0k_0} +$*

$\overline{T}_{1k_0i}, t_{1k_02a})$:

$$0 < \pi_{yi} < \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{yi},$$

where $\overline{T}_{1k_0i}$ *depends only on the model parameters,* Δ *and* ϵ.

Proof. We have shown above that for t in (t_{0k_0}, t_{1k_02a}) we have that $\pi_{h_1i}(t) \leq \frac{1}{2}\ \epsilon\pi^*_{h_1i}$ for $i = 1, 2, \ldots p$. From equation (2.5) we have:

$$\begin{aligned} \frac{d}{dt}\Big[\pi_{yi}\exp(\mu t)\Big] &= \sigma\pi_{h_1i}\exp(\mu t), \\ &\leq \frac{1}{2}\sigma\ \epsilon\pi^*_{h_1i}\exp(\mu t). \end{aligned}$$

Integrating over $[t_{0k_0}, t]$ for $t \leq t_{1k_02a}$:

$$\begin{aligned} \pi_{yi}(t) &\leq \pi_{yi}(t_{0k_0})\exp[-\mu(t - t_{0k_0})] + \frac{1}{2}\frac{\sigma}{\mu}\ \epsilon\pi^*_{h_1i}, \\ &\leq \exp[-\mu(t - t_{0k_0})] + \frac{1}{2}\frac{\sigma}{\mu}\ \epsilon\pi^*_{h_1i}, \\ &= \exp[-\mu(t - t_{0k_0})] + \frac{1}{2}\ \epsilon\pi^*_{yi}. \end{aligned}$$

Thus, taking t sufficiently large, say $t \geq t_{0k_0} + \overline{T}_{1k_0i}$ completes the proof.

$$\pi_{yi}(t) \leq \Big(\frac{1}{2} + \Delta\Big)\ \epsilon\pi^*_{yi},$$

where Δ is small and positive. □

Lemma 3.3.9. *For each* $i = 1, 2, \ldots p$, *there exists a time* $\overline{T}_{2k_0i} > 0$ *dependent only on the model parameters,* Δ *and* ϵ, *such that if* $t_{0k_0} + \overline{T}_{2k_0i} < t_{1k_02a}$, *then for all* $t \in [t_{0k_0} + \overline{T}_{2k_0i}, t_{1k_02a})$:

$$0 < \pi_{h_2i} < \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{h_2i}.$$

Proof. We use a similar method as in the proof of Lemma 3.8 of Corson et al. (2012). Define $x_i = \frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}$. From the proof of Lemma 3.1.6 we have:

$$\frac{d}{dt}\Big(\frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}\Big) = \frac{d}{dt}(x_i) = -(\mu+\sigma)\Big(\frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}\Big).$$

Hence:

$$x_i(t) = x_i(0)e^{-(\mu+\sigma)t},$$

and

$$\begin{aligned}
\big|x_i(t)\big| &= \big|x_i(0)\big|e^{-(\mu+\sigma)t}, \\
&\leq \Big|\frac{\pi_{h_1 i}(0)}{1-\delta} - \frac{\pi_{h_2 i}(0)}{\delta}\Big|e^{-(\mu+\sigma)t}, \\
&\leq \Big|\frac{\pi_{h_1 i}(0)}{1-\delta} + \frac{\pi_{h_2 i}(0)}{\delta}\Big|e^{-(\mu+\sigma)t}, \\
&= \Big|\frac{\delta\pi_{h_1 i}(0) + (1-\delta)\pi_{h_2 i}(0)}{\delta(1-\delta)}\Big|e^{-(\mu+\sigma)t}.
\end{aligned}$$

As $\pi_{h_1 i}(0) \leq 1$ and $\pi_{h_2 i}(0) \leq 1$, then we have:

$$\big|x_i(t)\big| \leq \frac{e^{-(\mu+\sigma)t}}{\delta(1-\delta)}.$$

Thus:

$$\begin{aligned}
\frac{\pi_{h_2 i}}{\delta} &\leq \frac{e^{-(\mu+\sigma)t}}{\delta(1-\delta)} + \frac{\pi_{h_1 i}}{1-\delta}, \\
\pi_{h_2 i} &\leq \frac{e^{-(\mu+\sigma)t}}{1-\delta} + \frac{\delta\pi_{h_1 i}}{1-\delta}.
\end{aligned}$$

As we know that for $i = 1, 2, \ldots p$ $\pi_{h_1 i} < \frac{1}{2}\epsilon\pi^*_{h_1 i}$, so in $[t_{0k_0}, t_{1k_0 2a}]$ we have that:

$$\pi_{h_2 i} \leq \frac{1}{2}\epsilon\pi^*_{h_2 i} + \frac{e^{-(\mu+\sigma)t}}{\delta(1-\delta)},$$

taking t sufficiently large will complete the proof. □

Lemma 3.3.10. *For each $i = 1, 2, \ldots p$, there exists a time $\overline{T}_{3k_0 i} > 0$ dependent only on the model parameters, Δ and ϵ, such that for $t \in [t_{0k_0} + \overline{T}_{2k_0 i} + \overline{T}_{3k_0 i}, t_{1k_0 2a})$:*

$$0 < \pi_{zi} < \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\pi^*_{zi}.$$

Proof. We write equation (2.6) as:

$$\frac{d}{dt}\big[\pi_{zi}\exp(\mu t)\big] \;=\; \sigma\alpha\pi_{h_2 i}\exp(\mu t).$$

From Lemma 3.3.9 we have shown that, for $t \in [t_{0k_0} + \overline{T}_{2k_0 i}, t_{1k_0 2a})$, $\pi_{h_2 i} \leq (\frac{1}{2} + \Delta)\epsilon\pi^*_{h_2 i}$ hence:

$$\frac{d}{dt}\big[\pi_{zi}\exp(\mu t)\big] \;\leq\; \Big(\frac{1}{2} + \Delta\Big)\epsilon\sigma\alpha\pi^*_{h_2 i}\exp(\mu t).$$

Integrating over $[t_{0k_0} + \overline{T}_{2k_0 i}, t]$ gives:

$$\pi_{zi}(t) \leq \exp[-\mu(t - t_{0k_0} - \overline{T}_{2k_0 i})] + \Big(\frac{1}{2} + \Delta\Big)\epsilon\frac{\sigma\alpha}{\mu}\pi^*_{h_2 i}.$$

Then, provided that t is large enough, $t \in [t_{0k_0} + \overline{T}_{2k_0 i} + \overline{T}_{3k_0 i}, t_{1k_0 2a}]$

$$\pi_{zi}(t) \leq \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\pi^*_{zi},$$

and the result holds. $\overline{T}_{3k_0i}$ depends only on the model parameters, ϵ and Δ. $\square$

Define

$$\begin{aligned} \overline{T}_{1k_0} &= \max_{i\in\{1,2,\ldots p\}} T_{1k_0i}, \\ \overline{T}_{2k_0} &= \max_{i\in\{1,2,\ldots p\}} T_{2k_0i}, \\ \text{and} \qquad \overline{T}_{3k_0} &= \max_{i\in\{1,2,\ldots p\}} T_{3k_0i}. \end{aligned}$$

Using the needles' model equations (2.7)-(2.9) together with Lemmas 3.3.8, 3.3.9 and 3.3.10, we have that for $j = 1, 2 \ldots q$ then there exists a $\overline{T}_{4k_0j} > 0$, such that for $t_{1k_02a} \geq t \geq t_{0k_0} + \overline{T}_{4k_0j} > 0$, $(\frac{1}{2} + \Delta)\epsilon\beta^*_{h_1j} > \beta_{h_1j} > 0$. Similarly there exists a $\overline{T}_{5k_0j} > 0$, such that for $t_{1k_02a} \geq t \geq t_{0k_0} + \overline{T}_{2k_0} + \overline{T}_{5k_0j} > 0$, $(\frac{1}{2} + 2\Delta)\epsilon\beta^*_{h_2j} > \beta_{h_2j} > 0$. Finally, there exists a $\overline{T}_{6k_0j} > 0$, such that for $t_{1k_02a} \geq t \geq t_{0k_0} + \overline{T}_{1k_0} + \overline{T}_{6k_0} > 0$, $(\frac{1}{2} + 2\Delta)\epsilon\beta^*_{yj} > \beta_{yj} > 0$. Moreover, $\overline{T}_{4k_0j}$, $\overline{T}_{5k_0j}$, and $\overline{T}_{6k_0j}$ are all dependent only on the model parameters, ϵ and Δ, not the initial conditions. Now we define:

$$\begin{aligned} \overline{T}_{4k_0} &= \max_{j\in\{1,2,\ldots q\}} \overline{T}_{4k_0j}, \\ \overline{T}_{5k_0} &= \max_{j\in\{1,2,\ldots q\}} \overline{T}_{5k_0j}, \\ \text{and} \qquad \overline{T}_{6k_0} &= \max_{j\in\{1,2,\ldots q\}} \overline{T}_{6k_0j}. \end{aligned}$$

Although we have shown that, as each π_{h_1i}, for $i = 1, 2 \ldots p$, becomes small, then all other variables become small too, we now attempt to show that all other π_{h_1i} cannot become arbitrary small. We shall do this by showing that $t_{1k_02a} - t_{0k_0}$ can be bounded above by a fixed finite value and hence all π_{h_1i} cannot remain beneath $\frac{1}{2}\ \epsilon\pi^*_{h_1i}$ long enough to become arbitrarily close to the origin. There are two possi-

bilities: first each $\pi_{h_1 i}$ stays beneath $\frac{1}{2}\ \epsilon\pi^*_{h_1 i}$ long enough for all the other variables to become small or some rise above $\frac{1}{2}\ \epsilon\pi^*_{h_1 i}$ before all other variables have become small. Hence, either:

(i) $t_{1k_02a} \geq t_{0k_0} + \max[\overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}, \overline{T}_{4k_0}, \overline{T}_{2k_0} + \overline{T}_{5k_0}, \overline{T}_{1k_0} + \overline{T}_{6k_0}]$; or

(ii) $t_{1k_02a} < t_{0k_0} + \max[\overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}, \overline{T}_{4k_0}, \overline{T}_{2k_0} + \overline{T}_{5k_0}, \overline{T}_{1k_0} + \overline{T}_{6k_0}]$.

Now we aim to show that $t_{1k_02a} - t_{0k_0} < T_{k_02a}$ where T_{k_02a} is a finite value depending only on the model parameters, Δ and ϵ. If (ii) holds then some $\pi_{h_1 i}$ rises above $\frac{1}{2}\ \epsilon\pi^*_{h_1 i}$ before all other variables have become small, and the result is proved. Here we deal with the first case where t_{1k_02a} occurs at a time bigger than or equal to the time that it takes for all other terms to become small. By using the result of the instability of the disease-free equilibrium when $R_0 > 1$ we shall show that $\pi_{h_1 i}$ cannot become arbitrarily small.

Lemma 3.3.11. *Suppose that $\pi_{h_1 k_0}(\Delta t) \geq \frac{1}{2}\ \epsilon\pi^*_{h_1 k_0}$. If all $\pi_{h_1 i}(t)$ $i = 1, 2, \ldots p$ are beneath $\frac{1}{2}\ \epsilon\pi^*_{h_1 i}$ just beyond time t_{0k_0} then at least one $\pi_{h_1 i}(t)$ returns to the level $\frac{1}{2}\ \epsilon\pi^*_{h_1 i}$ by time at least $t_{1k_02a} = t_{0k_0} + \max[\overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0} + \overline{T}_{7k_0}, \overline{T}_{4k_0}, \overline{T}_{2k_0} + \overline{T}_{5k_0}, \overline{T}_{1k_0} + \overline{T}_{6k_0}]$, which is finite and depends only on the model parameters, Δ and ϵ.*

Proof. To prove this lemma we follow the proof of Lemma 3.10 of Corson et al. (2012). Assume that ϵ_2 is real and positive where $0 < \epsilon_2 < 1$ and consider the matrix $\mathbf{J}(\epsilon_2)$ given by:

$$\boldsymbol{J}(\epsilon_2) = \begin{pmatrix} \boldsymbol{K} & \boldsymbol{S} \\ \boldsymbol{M} & \boldsymbol{N} \end{pmatrix},$$

where $\boldsymbol{K}, \boldsymbol{M}$ and $\boldsymbol{N}$ are defined as in the proof of Theorem 3.2.1 (the instability of the disease-free equilibrium), and

$$\boldsymbol{S} = \begin{pmatrix} \boldsymbol{S}_{11} & \boldsymbol{S}_{12} & \dots & \boldsymbol{S}_{1q} \\ \boldsymbol{S}_{21} & \boldsymbol{S}_{22} & \dots & \boldsymbol{S}_{2q} \\ \vdots & \vdots & \ddots & \vdots \\ \boldsymbol{S}_{p1} & \boldsymbol{S}_{p2} & \dots & \boldsymbol{S}_{pq} \end{pmatrix}.$$

Here for $i = 1, 2, \dots p$, $j = 1, 2, \dots q$,

$$\boldsymbol{S}_{ij} = \begin{bmatrix} 0 & 0 & 0 \\ (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_y(1-\epsilon_2) \\ \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_y(1-\epsilon_2) \\ 0 & 0 & 0 \end{bmatrix}.$$

In other words $\boldsymbol{S} = (1-\epsilon_2)\boldsymbol{L}$ where $\boldsymbol{L}$ was defined in the proof of Theorem 3.2.1. Denote the eigenvalues of $\boldsymbol{J}(\epsilon_2)$ by $\omega_s(\epsilon_2)$ for $s = 1, 2, \dots 4p+3q$. Analogously to the argument for the instability of the disease-free equilibrium, we define the matrix

$$\hat{\boldsymbol{J}}(\epsilon_2) = \begin{pmatrix} \hat{\boldsymbol{K}} & \hat{\boldsymbol{S}} \\ \hat{\boldsymbol{M}} & \hat{\boldsymbol{N}} \end{pmatrix},$$

where $\hat{\boldsymbol{K}}, \hat{\boldsymbol{M}}$ and $\hat{\boldsymbol{N}}$ are defined in the proof of the instability of the disease-free equilibrium:

$$\hat{\boldsymbol{S}} = \begin{pmatrix} \hat{\boldsymbol{S}}_{11} & \hat{\boldsymbol{S}}_{12} & \dots & \hat{\boldsymbol{S}}_{1q} \\ \hat{\boldsymbol{S}}_{21} & \hat{\boldsymbol{S}}_{22} & \dots & \hat{\boldsymbol{S}}_{2q} \\ \vdots & \vdots & \ddots & \vdots \\ \hat{\boldsymbol{S}}_{p1} & \hat{\boldsymbol{S}}_{p2} & \dots & \hat{\boldsymbol{S}}_{pq} \end{pmatrix},$$

where for $i = 1, 2, \ldots p$ and $j = 1, 2, \ldots q$ then $\hat{\boldsymbol{S}}_{ij} =$

$$\begin{bmatrix} (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & (1-\delta)\lambda_i P_{ij}(1-\phi_{ij})\alpha_y(1-\epsilon_2) \\ \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_h(1-\epsilon_2) & \delta\lambda_i P_{ij}(1-\phi_{ij})\alpha_y(1-\epsilon_2) \\ 0 & 0 & 0 \end{bmatrix},$$

so $\hat{\boldsymbol{S}} = (1-\epsilon_2)\hat{\boldsymbol{L}}$ where $\hat{\boldsymbol{L}}$ is defined in the proof of Theorem 3.2.1. Now we re-order the rows and columns of $\boldsymbol{J}(\epsilon_2)$ so that $\omega_s(\epsilon_2) = -\mu$ for $s = 3p + 3q + 1, 3p + 3q + 2, \ldots 4p + 3q$. Then the remaining $3p + 3q$ eigenvalues of $\boldsymbol{J}(\epsilon_2)$ are the eigenvalues of $\hat{\boldsymbol{J}}(\epsilon_2)$. Moreover, from Lemma 3.2.2 if M is large and positive then $\hat{\boldsymbol{J}}(\epsilon_2) + M\boldsymbol{I}$ is an irreducible matrix of dimension $(3p+3q) \times (3p+3q)$ with eigenvalues $\omega_s(\epsilon_2) + M$ for $s = 1, 2 \ldots 3p + 3q$. As in Corson et al. (2012), Lemma 2.1 of Nold (1980) implies that the characteristic equation of $\hat{\boldsymbol{J}}(\epsilon_2) + M\boldsymbol{I}$ has a non-repeated real root that is the spectral radius eigenvalue of $\hat{\boldsymbol{J}}(\epsilon_2) + M\boldsymbol{I}$. If this root is denoted by $M + \omega_1(\epsilon_2)$ then all other eigenvalues have smaller real part, so $\omega_1(\epsilon_2)$ is real and all the other eigenvalues of $\hat{\boldsymbol{J}}(\epsilon_2)$ have strictly smaller real parts. This also holds even if $\epsilon_2 = 0$. Moreover as $\epsilon_2 \longrightarrow 0$, $\omega_1(\epsilon_2) \longrightarrow \omega_1(0)$ and we know that $\omega_1(0) > 0$ if $R_0 > 1$ as we have shown the instability of the disease-free equilibrium. So we can choose $\epsilon_2 > 0$ small enough so that $\omega_1(\epsilon_2) > 0$.

Without loss of generality we assume that $0 < \epsilon_2 < 1$. We choose ϵ small enough so that for $i = 1, 2, \ldots p$:

$$\frac{1}{2}\,\epsilon\pi^*_{h_1 i} + \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{h_2 i} + \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{yi} + \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\pi^*_{zi} < \epsilon_2, \tag{3.41}$$

for $t_{1k_0 2a} > t > t_{0k_0} + \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}$ we have that $\pi^\dagger_i(t) = \pi_{h_1 i} + \pi_{h_2 i} + \pi_{yi} + \pi_{zi} < \epsilon_2$

for $i = 1, 2, \ldots p$. For $i = 1, 2, \ldots p$ define $t_{2k_0 i} = \inf\{\zeta \geq 0$: for $t_{1k_0 2a} > t > t_{0k_0} + \zeta, \pi_i(t) < \epsilon_2\}$. So if $t_{2k_0 i} > 0$ then by continuity $\pi_i(t_{0k_0} + t_{2k_0 i}) = \epsilon_2$ and $t_{2k_0 i}$ is the last time before $t_{1k_0 2a}$ that $\pi_i(t) \geq \epsilon_2$. Note that for $i = 1, 2, \ldots p$, $t_{2k_0 i} \leq \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}$. If $t_{1k_0 2a} < t_{0k_0} + \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}$ there is nothing to prove so consider the case where $t_{1k_0 2a} > t_{0k_0} + \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}$. For $t_{1k_0 2a} > t > t_{0k_0} + \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}$ we have that:

$$\frac{d\boldsymbol{x}}{dt} \geq \hat{\boldsymbol{J}}(\epsilon_2)\boldsymbol{x},$$

where $\boldsymbol{x} = \big(\pi_{h_1 1}(t), \pi_{h_2 1}(t), \pi_{y1}(t), \pi_{h_1 2}(t), \pi_{h_2 2}(t), \pi_{y2}(t), \ldots, \pi_{h_1 p}(t), \pi_{h_2 p}(t), \pi_{yp}(t),$ $\beta_{h_1 1}(t), \beta_{h_2 1}(t), \beta_{y1}(t), \beta_{h_1 2}(t), \beta_{h_2 2}(t), \beta_{y2}(t), \ldots, \beta_{h_1 q}(t), \beta_{h_2 q}(t), \beta_{yq}(t)\big)$. From Lemma 2.1 of Nold (1980) we have that for M sufficiently large and positive $M\boldsymbol{I} + \hat{\boldsymbol{J}}(\epsilon_2)$ has a strictly positive left eigenvector $\boldsymbol{e}$ which corresponds to the spectral radius $M + \omega_1(\epsilon_2)$ of $M\boldsymbol{I} + \hat{\boldsymbol{J}}(\epsilon_2)$. Hence $\boldsymbol{e}$ is also a left eigenvector of $\hat{\boldsymbol{J}}(\epsilon_2)$.

Thus for $t_{1k_0 2a} > t > t_{0k_0} + \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}$ we have that:

$$\begin{aligned} \boldsymbol{e} \cdot \frac{d\boldsymbol{x}}{dt} &\geq \boldsymbol{e}\hat{\boldsymbol{J}}(\epsilon_2)\boldsymbol{x}, \\ &\geq \omega_1(\epsilon_2)\boldsymbol{e} \cdot \boldsymbol{x}. \end{aligned}$$

For each $i = 1, 2, \ldots p$, integrating over $[t_{0k_0} + t_{2k_0 i}, t]$ we deduce that for $t \geq t_{0k_0} + t_{2k_0 i}$:

$$\boldsymbol{e} \cdot \boldsymbol{x}(t) \geq (\boldsymbol{e} \cdot \boldsymbol{x})(t_{0k_0} + t_{2k_0 i}) \exp[\omega_1(\epsilon_2)(t - t_{0k_0} - t_{2k_0 i})],$$

so if for some $i_0 \in \{1, 2, \ldots p\},\ t_{2k_0 i_0} > 0$, we have:

$$\boldsymbol{e} \cdot \boldsymbol{x}(t) \geq \pi_i(t_{0k_0} + t_{2k_0 i_0})\epsilon_2 \min(e_{3i_0-2}, e_{3i_0-1}, e_{3i_0}) \exp[\omega_1(\epsilon_2)(t - t_{0k_0} - t_{2k_0 i_0})].$$

On the other hand if $t_{2k_0 i} = 0$ for $i = 1, 2, \ldots p$ and $\pi_{h_1 k_0}(\Delta t) \geq \frac{1}{2}\ \epsilon\pi^*_{h_1 k_0}$, so that $\pi_{h_1 k_0}(t_{0k_0}) = \frac{1}{2}\ \epsilon\pi^*_{h_1 k_0}$

$$\boldsymbol{e} \cdot \boldsymbol{x}(t) > \frac{1}{2}\ \epsilon\pi^*_{h_1 k_0} \min(e_{3k_0-2}, e_{3k_0-1}, e_{3k_0}) \exp[\omega_1(\epsilon_2)(t - t_{0k_0} - t_{2k_0 i_0})].$$

Hence, if $t_{2k_0 i_0} > 0$ for some i_0 we define $t_{2k_0} = t_{2k_0 i_0}$. On the other hand if $t_{2k_0 i} = 0$ for $i = 1, 2, \ldots p$ and $\pi_{h_1 k_0}(\Delta t) \geq \frac{1}{2}\ \epsilon\pi^*_{h_1 k_0}$, then we define $t_{2k_0} = 0$. Then after a time $t_{0k_0} + t_{2k_0} + \overline{T}_{7k_0}$ where $\overline{T}_{7k_0}$ depends only on the model parameters, $\epsilon,\ \epsilon,\ \epsilon_2$ and Δ

$$\begin{aligned}
\boldsymbol{e} \cdot \boldsymbol{x}(t) \quad > \quad \boldsymbol{e} \cdot \Bigg(& \frac{1}{2}\ \epsilon\pi^*_{h_1 1}, \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{h_2 1}, \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{y1}, \frac{1}{2}\ \epsilon\pi^*_{h_1 2}, \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{h_2 2}, \\
& \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{y2}, \ldots, \frac{1}{2}\ \epsilon\pi^*_{h_1 p}, \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{h_2 p}, \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{yp}, \Big(\frac{1}{2} + \Delta\Big)\epsilon\beta^*_{h_1 1}, \\
& \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\beta^*_{h_2 1}, \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\beta^*_{y1}, \Big(\frac{1}{2} + \Delta\Big)\epsilon\beta^*_{h_1 2}, \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\beta^*_{h_2 2}, \\
& \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\beta^*_{y2}, \ldots, \Big(\frac{1}{2} + \Delta\Big)\epsilon\beta^*_{h_1 q}, \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\beta^*_{h_2 q}, \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\beta^*_{yq} \Bigg).
\end{aligned} \tag{3.42}$$

But if $t_{1k_0 2a} \geq t \geq t_{0k_0} + \max[\overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}, \overline{T}_{4k_0}, \overline{T}_{2k_0} + \overline{T}_{5k_0}, \overline{T}_{1k_0} + \overline{T}_{6k_0}, t_{2k_0} + \overline{T}_{7k_0}]$, then for $i = 1, 2, \ldots p$ and $j = 1, 2, \ldots q$ $\pi_{h_1 i} \leq \frac{1}{2}\ \epsilon\pi^*_{h_1 i}$, $\pi_{h_2 i} \leq \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{h_2 i}$, $\pi_{yi} \leq \Big(\frac{1}{2} + \Delta\Big)\epsilon\pi^*_{yi}$, $\pi_{zi} \leq \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\pi^*_{zi}$, $\beta_{h_1 j} \leq \Big(\frac{1}{2} + \Delta\Big)\epsilon\beta^*_{h_1 j}$, $\beta_{h_2 j} \leq \Big(\frac{1}{2} + 2\Delta\Big)\epsilon\beta^*_{h_2 j}$

and $\beta_{yj} \leq \left(\frac{1}{2} + 2\Delta\right)\epsilon\beta^*_{yj}$ all are true, which implies that

$$\begin{aligned}
\boldsymbol{e}\cdot\boldsymbol{x}(t) \;\leq\; \boldsymbol{e}\cdot\Bigg(&\frac{1}{2}\,\epsilon\pi^*_{h_1 1}, \left(\frac{1}{2}+\Delta\right)\epsilon\pi^*_{h_2 1}, \left(\frac{1}{2}+\Delta\right)\epsilon\pi^*_{y1}, \frac{1}{2}\,\epsilon\pi^*_{h_1 2}, \left(\frac{1}{2}+\Delta\right)\epsilon\pi^*_{h_2 2},\\
&\left(\frac{1}{2}+\Delta\right)\epsilon\pi^*_{y2}, \ldots, \frac{1}{2}\,\epsilon\pi^*_{h_1 p}, \left(\frac{1}{2}+\Delta\right)\epsilon\pi^*_{h_2 p}, \left(\frac{1}{2}+\Delta\right)\epsilon\pi^*_{yp}, \left(\frac{1}{2}+\Delta\right)\epsilon\beta^*_{h_1 1},\\
&\left(\frac{1}{2}+2\Delta\right)\epsilon\beta^*_{h_2 1}, \left(\frac{1}{2}+2\Delta\right)\epsilon\beta^*_{y1}, \left(\frac{1}{2}+\Delta\right)\epsilon\beta^*_{h_1 2}, \left(\frac{1}{2}+2\Delta\right)\epsilon\beta^*_{h_2 2},\\
&\left(\frac{1}{2}+2\Delta\right)\epsilon\beta^*_{y2}, \ldots, \left(\frac{1}{2}+\Delta\right)\epsilon\beta^*_{h_1 q}, \left(\frac{1}{2}+2\Delta\right)\epsilon\beta^*_{h_2 q}, \left(\frac{1}{2}+2\Delta\right)\epsilon\beta^*_{yq}\Bigg).
\end{aligned} \tag{3.43}$$

From (3.42) and (3.43) we have a contradiction. Therefore

$$\begin{aligned}
t_{1k_0 2a} &< t_{0k_0} + \max[\overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0}, \overline{T}_{4k_0}, \overline{T}_{2k_0} + \overline{T}_{5k_0}, \overline{T}_{1k_0} + \overline{T}_{6k_0}, t_{2k_0} + \overline{T}_{7k_0}],\\
&< t_{0k_0} + \max[\overline{T}_{4k_0}, \overline{T}_{2k_0} + \overline{T}_{5k_0}, \overline{T}_{1k_0} + \overline{T}_{6k_0}, \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0} + \overline{T}_{7k_0}].
\end{aligned}$$

Hence we have shown that if all $\pi_{h_1 i}(t)$ for $i = 1, 2, \ldots p$ are beneath $\frac{1}{2}\,\epsilon\pi^*_{h_1 i}$ just beyond time t_{0k_0}, then at least one $\pi_{h_1 i}(t)$ returns to the level $\frac{1}{2}\,\epsilon\pi^*_{h_1 i}$ by time at least $t_{0k_0} + \max[\overline{T}_{4k_0}, \overline{T}_{2k_0} + \overline{T}_{5k_0}, \overline{T}_{1k_0} + \overline{T}_{6k_0}, \overline{T}_{1k_0} + \overline{T}_{2k_0} + \overline{T}_{3k_0} + \overline{T}_{7k_0}]$, which is finite and depends only on the model parameters, ϵ and Δ. □

Case 2b:

$$S_1(t_{k_0} + \Delta t) \neq \emptyset.$$

This implies that for some $i \in \{1, 2, \ldots p\}$ and Δt small enough $\pi_{h_1 i}(t_{0k_0} + \Delta t) \geq \frac{1}{2}\,\epsilon\pi^*_{h_1 i}$. Let $t_{1k_0 2b}$ to be the next time after t_{0k_0} but before t_{1k_0} where $S_1(t_{1k_0 2b} + \Delta t) = \emptyset$. If $S_1(t) \neq \emptyset$ in $[t_{0k_0}, t_{1k_0}]$ we deduce that $t_{1k_0} = t_{1k_0 2b}$.

Lemma 3.3.12. *Suppose that $\Delta > 0$ is small and positive. Then there exists T_{1k_0}*

dependent only on the model parameters, Δ and ϵ, not on the initial conditions, such that for $t \in [t_{0k_0} + T_{1k_0}, t_{1k_0}]$,

$$0 < \pi_{yk_0} < \left(\frac{1}{2} + \Delta\right) \epsilon\pi^*_{yk_0}.$$

Proof. This is proved using a similar argument as in the proof of Lemma 3.3.8. We know that $\pi_{h_1k_0} \leq \frac{1}{2}\ \epsilon\pi^*_{h_1k_0}$ in (t_{0k_0}, t_{1k_1}) and from equation (2.5) we have:

$$\frac{d}{dt}[\pi_{yk_0} \exp(\mu t)] = \sigma\pi_{h_1k_0} \exp(\mu t).$$

The result follows by a similar argument as in the proof of Lemma 3.3.8. □

Lemma 3.3.13. *There exists T_{2k_0} dependent only on the model parameters, Δ and ϵ, not on the initial conditions, such that for $t \in [t_{0k_0} + T_{2k_0}, t_{1k_0}]$,*

$$0 < \pi_{h_2k_0} < \left(\frac{1}{2} + \Delta\right) \epsilon\pi^*_{h_2k_0}.$$

Proof. Similar to the proof of Lemma 3.3.9. □

Lemma 3.3.14. *There exists T_{3k_0} dependent only on the model parameters, Δ and ϵ, not on the initial conditions, such that for $t \in [t_{0k_0} + T_{2k_0} + T_{3k_0}, t_{1k_0}]$,*

$$0 < \pi_{zk_0} < \left(\frac{1}{2} + 2\Delta\right) \epsilon\pi^*_{zk_0}.$$

Proof. Similar to the proof of Lemma 3.3.10. □

Hence for $t \in [t_{0k_0} + T_{1k_0} + T_{2k_0} + T_{3k_0}, t_{1k_0}]$

$$\begin{aligned} \pi_{xk} + \pi_{x_1k} &= 1 - \pi_{h_1k} - \pi_{h_2k} - \pi_{yk} - \pi_{zk}, \\ &\geq \frac{1}{2}, \end{aligned}$$

if Δ and ϵ are small enough.

By Assumption A1 for $i_0 \in \{1, 2, \ldots p\}$, there exists j_0 with

$$P_{k_0j_0}(1 - \phi_{k_0j_0})\Lambda_{i_0j_0} > 0.$$

Then for $i_0 \in S_1(t)$

$$\begin{aligned} \frac{d\beta_{h_1j_0}}{dt} &\geq \Lambda_{i_0j_0}\frac{1}{2}\epsilon\pi^*_{h_1i_0} - \beta_{h_1j_0}\Big(\sum_{i=1}^{p}\Lambda_{ij} + \tau_j\Big), \\ &\geq \frac{1}{2}\,\epsilon \min_{i_0\in\{1,2,\ldots p\}} \Lambda_{i_0j_0}\pi^*_{h_1i_0} - \beta_{h_1j_0} \max_{j_0\in\{1,2,\ldots q\}} \Big(\sum_{i=1}^{p}\Lambda_{ij} + \tau_j\Big). \end{aligned}$$

We write $A = \frac{1}{2}\,\epsilon \min_{i_0\in\{1,2,\ldots p\}} \Lambda_{i_0j_0}\pi^*_{h_1i_0}$ and $B = \max_{j_0\in\{1,2,\ldots q\}} \Big(\sum_{i=1}^{p}\Lambda_{ij} + \tau_j\Big)$. Hence, we can rewrite the above inequality as:

$$\frac{d}{dt}(\beta_{h_1j_0}\exp(Bt)) \geq A\exp(Bt).$$

Integrating over $[t_{0k_0}, t)$

$$\begin{aligned} \beta_{h_1j_0}(\exp(Bt)) - \beta_{h_1j_0}(t_{0k_0}) &\geq \frac{A}{B}\Big(\exp(Bt) - \exp(Bt_{0k_0})\Big), \\ \beta_{h_1j_0} &\geq \frac{A}{B}\Big(1 - \exp[-B(t - t_{0k_0})]\Big), \end{aligned}$$

so there exists T_{4k_0} depending only on the model parameters, not on the initial conditions, such that for $t \in [t_{0k_0} + T_{4k_0}, t_{1k_02b}]$

$$\beta_{h_1 j_0} \geq \frac{A}{2B}.$$

Now for $t \in [t_{0k_0} + T_{1k_0} + T_{2k_0} + T_{3k_0} + T_{4k_0}, t_{1k_02b}]$ then we deduce that:

$$\begin{aligned} \frac{d}{dt}(\pi_{h_1 k_0}) &\geq (1-\delta)\lambda_{k_0} P_{k_0 j_0}(1-\phi_{k_0 j_0})\alpha_h \frac{A}{4B} - (\mu+\sigma)\pi_{h_1 k_0}, \\ &\geq C - (\mu+\sigma)\pi_{h_1 k_0}. \end{aligned}$$

Here

$$C = (1-\delta)\alpha_h \lambda_{k_0} \frac{A}{4B} \min_{j_0 \in X} \Big(P_{k_0 j}(1-\phi_{k_0 j}) \Big),$$

and X is the set $\{j \in \{1, 2, \ldots q\} : \text{such that } P_{k_0 j}(1-\phi_{k_0 j}) > 0\}$. Hence, we have that:

$$\begin{aligned} \pi_{h_1 k_0}(t) &\geq \pi_{h_1 k_0}(t_{0k_0} + T_{1k_0} + T_{2k_0} + T_{3k_0} + T_{4k_0}) \exp\Big[-(\mu+\sigma)(t - t_{0k_0} - T_{1k_0} \\ &\quad -T_{2k_0} - T_{3k_0} - T_{4k_0}) \Big] \\ &\quad + \frac{C}{\mu+\sigma} \left(1 - \exp[-(\mu+\sigma)(t - t_{0k_0} - T_{1k_0} - T_{2k_0} - T_{3k_0} - T_{4k_0})] \right), \\ &\geq \frac{1}{2} \frac{C}{\mu+\sigma}, \end{aligned}$$

for time $t \geq t_{0k_0+} + T_{1k_0} + T_{2k_0} + T_{3k_0} + T_{4k_0} + T_{5k_0}$ where again T_{5k_0} depends only on the model parameters, Δ and ϵ. Therefore, in the time $[t_{0k_0}, t_{2k_02a}]$, we find that

$\pi_{h_1 k_0}(t)$ is bounded below by the value

$$\min\Big\{\frac{1}{2}\epsilon\pi^*_{h_1 k_0}\exp\Big[-(\mu+\sigma)(T_{1k_0}+T_{2k_0}+T_{3k_0}+T_{4k_0}+T_{5k_0})\Big], \frac{1}{2}\ \frac{C}{\mu+\sigma}\Big\}.$$

Here in Case 2b $\pi_{h_1 k_0}(t)$ is bounded below by this value in $[t_{0k_0}, t_{1k_0 2b}]$. After time $t_{1k_0 2b}$ we stop being in Case 2b and enter Case 2a.

Let us now consider Case 2a. We note that one of $\pi_{h_1 1}, \pi_{h_1 2}, \ldots \pi_{h_1 p}$ say $\pi_{h_1 i}$ eventually rises above the value $\frac{1}{2}\epsilon\pi^*_{h_1 i}$. If this is $\pi_{h_1 k_0}$ then the result follows from our previous results for Case 2a. Starting at $\frac{1}{2}\epsilon\pi^*_{h_1 i}$ at time t_{0k_0}, $\pi_{h_1 k_0}$ rises up again to the level $\frac{1}{2}\epsilon\pi^*_{h_1 i}$ and the time taken to do this can be bounded above by a quantity that depends on only the model parameters, ϵ and Δ.

On the other hand, suppose that it is $\pi_{h_1 i}$ $(i \neq k_0)$ that reaches the level $\frac{1}{2}\epsilon\pi^*_{h_1 i}$ at time T_{k_0}. Then the maximum rate of increase of $\pi_{h_1 i}$ is denoted by L where

$$L = \max_{i\in\{1,2,\ldots p\}}(1-\delta)\lambda_i q \max[\alpha_h, \alpha_y].$$

Choose $\Delta_1 = \frac{1}{2L}\epsilon\pi^*_{h_1 i}$, then we deduce that:

$$\pi_{h_1 i}(t) \ \geq \ \frac{1}{4}\epsilon\pi^*_{h_1 i} \qquad \text{for} \quad t \ \in \ [T_{k_0}-\Delta_1, T_{k_0}],$$

where

$$L \leq \frac{1}{4\Delta_1}\epsilon\pi^*_{h_1 i}.$$

Now we choose $\Delta_2 = \min_{i\in\{1,2,\ldots p\}} \frac{1}{4L}\epsilon\pi^*_{h_1 i}$. Then we have that:

$$\pi_{h_1 i} \geq \frac{1}{4}\epsilon\pi^*_{h_1 i}, \text{ in the time } [T_{k_0} - \Delta_2, T_{k_0}].$$

So not only does $\pi_{h_1 i}$ rise to the level $\frac{1}{2}\epsilon\pi^*_{h_1 i}$ at time T_{k_0}, it also rises to at least the level $\frac{1}{4}\epsilon\pi^*_{h_1 i}$ in the whole small time interval $[T_{k_0} - \Delta_2, T_{k_0}]$. We shall now use this to find a lower bound for $\pi_{h_1 k_0}(T_{k_0})$.

For t in the interval $[T_{k_0} - \frac{1}{2}\Delta_2, T_{k_0}]$, we have:

$$\beta_{h_1 j_0}(t) \geq \min_{i_0\in\{1,2,\ldots p\}} \Lambda_{i_0 j_0}\frac{1}{4}\epsilon\pi^*_{h_1 i_0}\left(\frac{1 - \exp\Big[-\max_{j\in\{1,2,\ldots q\}}(\sum_{i=1}^p \Lambda_{ij} + \tau_j)\frac{1}{2}\Delta_2\Big]}{\max_{j\in\{1,2,\ldots q\}}(\sum_{i=1}^p \Lambda_{ij} + \tau_j)}\right).$$

We obtain that

$$\pi_{h_1 k_0}(T_{k_0}) \geq \frac{A'}{\mu+\sigma}\left(1 - \exp\Big[-(\mu+\sigma)\frac{1}{2}\Delta_2\Big]\right),$$

where $A' = \min_{i_0, k_0\in\{1,2,\ldots p\}} A''(i_0, k_0)$. Here

$$\begin{aligned} A''(i_0, k_0) &= \Big(\frac{1}{4}\Big)\frac{(1-\delta)\lambda_{k_0}P_{k_0 j_0}(1-\phi_{k_0 j_0})\alpha_h\Lambda_{i_0 j_0}\epsilon\pi^*_{h_1 i_0}}{\max_{j\in\{1,2,\ldots q\}}(\sum_{i=1}^p \Lambda_{ij} + \tau_j)} \\ &\quad \times\left(1 - \exp\Big[-\max_{j\in\{1,2,\ldots q\}}\Big(\sum_{i=1}^p \Lambda_{ij} + \tau_j\Big)\Big(\frac{1}{2}\Delta_2\Big)\Big]\right). \end{aligned}$$

This illustrates that

$$\pi_{h_1 k_0}(T_{k_0}) \geq A^*,$$

where $A^* = \frac{A'}{\mu+\sigma}\Big(1 - \exp\Big[(\mu+\sigma)\frac{1}{2}\Delta_2\Big]\Big) > 0$.

Hence, the process alternates between Case 2a and Case 2b. Suppose that the process starts in Case 2a. On leaving Case 2a at time $T_{k_0 2a}$ we have that:

$$\pi_{h_1 k_0}(T_{k_0 2a}) \geq A^*.$$

Note that $A^* = \frac{1}{2} M_1 \epsilon \pi^*_{h_1 k_0}$, where M_1 is a constant independent of ϵ and Δ. If $M_1 \geq 1$ then $A^* \geq \frac{1}{2}\epsilon \pi^*_{h_1 k_0}$. So the argument for Case 2b above shows that on leaving Case 2b at time $T_{k_0 2b}$:

$$\pi_{h_1 k_0}(T_{k_0 2b}) \geq \min \left[\frac{1}{2} \epsilon \pi^*_{h_1 k_0} \exp[-(\mu+\sigma)(T_{1k_0}+T_{2k_0}+T_{3k_0}+T_{4k_0}+T_{5k_0})], \frac{C}{2(\mu+\sigma)} \right].$$

If $M_1 < 1$ then replacing ϵ by the smaller value $M_1 \epsilon$ in the argument for Case 2b shows that on leaving Case 2b at time $T_{k_0 2b}$:

$$\pi_{h_1 k_0}(T_{k_0 2b}) \geq \min \left[\frac{1}{2} M_1 \epsilon \pi^*_{h_1 k_0} \exp[-(\mu+\sigma)(T_{1k_0}+T_{2k_0}+T_{3k_0}+T_{4k_0}+T_{5k_0})], \frac{C}{2(\mu+\sigma)} \right].$$

Hence in either case on leaving Case 2b at time $T_{k_0 2b}$, $\pi_{h_1 k_0}(T_{k_0 2b}) \geq A^{**}$, where

$$A^{**} = \min \left[\frac{1}{2} \min(1, M_1) \epsilon \pi^*_{h_1 k_0} \exp[-(\mu+\sigma)(T_{1k_0}+T_{2k_0}+T_{3k_0}+T_{4k_0}+T_{5k_0})], \frac{C}{2(\mu+\sigma)} \right].$$

Now each subsequent time that the system leaves Case 2a at $T_{k_0 2an}$ say, $\pi_{h_1 k_0}(T_{k_0 2an}) \geq A^*$. Similarly each subsequent time that the system leaves Case 2b at time $T_{k_0 2bn}$ say, $\pi_{h_1 k_0}(T_{k_0 2bn}) \geq A^{**}$.

Hence the system alternates between Case 2a and Case 2b. The time between entering and leaving Case 2a is bounded above by a time $\overline{T}_{1a}$ which depends only on ϵ, Δ and the model parameters, although it may stay indefinitely in Case 2b after spending some time intervals in Case 2a. In the second and subsequent times in Case 2a the value on entering Case 2a will be at least A^{**} and a straightforward modification of the argument given for Case 2a shows that the second and subsequent times spent in this case the time between entering and leaving can be bounded above by a time $\overline{T}_{2a}$ which depends only on ϵ, Δ and the model parameters. Hence whilst it is in Case 2a $\pi_{h_1k_0}$ can be bounded below by:

$$\min\Big(\frac{1}{2}\,\epsilon\pi^*_{h_1k_0}\exp[-(\mu+\sigma)\overline{T}_{1a}], A^{**}\exp[-(\mu+\sigma)\overline{T}_{2a}]\Big).$$

In Case 2b $\pi_{h_1k_0}$ starts at a value of at least A^* and whilst it is in Case 2b $\pi_{h_1k_0}$ can be bounded below by

$$\min\left[\frac{1}{2}\min(1,M_1)\epsilon\pi^*_{h_1k_0}\exp[-(\mu+\sigma)(T_{1k_0}+T_{2k_0}+T_{3k_0}+T_{4k_0}+T_{5k_0})], \frac{C}{2(\mu+\sigma)}\right].$$

We deduce that $\pi_{h_1k_0,\infty} > 0$ which contradicts that $\pi_{h_1k_0,\infty} = 0$. This completes the proof of Theorem 3.3.7 if the system starts in Case 2b (and $\pi_{h_1k_0}(\Delta t) \geq \frac{1}{2}\epsilon\pi^*_{h_1k_0}$). A similar argument shows that the result of the theorem is true if the system starts in Case 2a (and $\pi_{h_1k_0}(\Delta t) \geq \frac{1}{2}\epsilon\pi^*_{h_1k_0}$). We now discuss the situation where $0 < \pi_{h_1k_0}(\Delta t) < \frac{1}{2}\epsilon\pi^*_{h_1k_0}$. We needed to assume that $\pi_{h_1k_0}(\Delta t) \geq \frac{1}{2}\epsilon\pi^*_{h_1k_0}$ to ensure that in Case 2a some $\pi_{h_1k_0}(\Delta t)$ rise to the level $\frac{1}{2}\epsilon\pi^*_{h_1i}$, in a time which could be bounded above by a time which depended only on the model parameters, ϵ and Δ.

Consider first the situation where the system starts in Case 2a. In this case the same argument (slightly modified) shows that eventually (in a finite time) some $\pi_{hi}(t)$ rises above the level $\frac{1}{2}\epsilon\pi^*_{h_1 i}$. On leaving Case 2a at time $T_{k_0 2a}$, $\pi_{h_1 k_0}(T_{k_0 2a}) \geq A^*$. The proof proceeds as in the case where $\pi_{h_1 k_0}(\Delta t) \geq \frac{1}{2}\epsilon\pi^*_{h_1 k_0}$.

If we start in Case 2b where $0 < \pi_{h_1 k_0}(\Delta t) \leq \frac{1}{2}\epsilon\pi^*_{h_1 k_0}$ then it is possible that the system remains in Case 2b indefinitely. Even in this case after a finite time

$$\pi_{h_1 k_0}(t) \geq \frac{C}{2(\mu + \sigma)}.$$

Thus Theorem 3.3.7 is again true. If the system leaves Case 2b for Case 2a in finite time then the argument for Case 2a above (now valid for $\pi_{h_1 k_0}(\Delta t) > 0$) shows that Theorem 3.3.7 is again true. □

In this section, we have discussed persistence of the disease. If $R_0 > 1$ and disease is initially present in at least one group of addicts or at least one shooting gallery, then, provided that an irreducibility condition is satisfied, the disease will ultimately persist in all groups of addicts and all needles. Moreover, the ultimate lower bound for the level of HCV in infected needles and addicts depends only on the model parameters not the initial conditions.

3.4 Conclusion

In this chapter we have investigated analytically the results and behaviour of our basic HCV transmission model. A key parameter of our model is the basic reproductive number R_0. We have shown that if $R_0 \leq 1$ then there is only the disease-free

equilibrium which is globally asymptotically stable. If $R_0 > 1$ and an irreducibility condition is satisfied, then the disease-free equilibrium is unstable and there is also a unique endemic equilibrium.

We also showed that if $R_0 > 1$ and the irreducibility condition is satisfied then the disease is ultimately persistent. The lower bound for the level of disease persistence in both addicts and needles depends only on the model parameters, not on the initial conditions.

This concludes the formal mathematical analysis of this model. In the next chapter we shall describe numerical simulations using our HCV transmission model. First we shall discuss parameter estimates in detail. Then a numerical study will verify the analytical results obtained in the first two chapters, namely the results that the disease will die out if $R_0 \leq 1$ and persist if $R_0 > 1$.

Later in Chapter Six we shall look numerically at the analytical results obtained previously which showed that R_0 was minimised by all groups of addicts visiting shooting galleries at the same rate. We shall also verify numerically our results on optimal control of HCV by allocation of limited amounts of needle exchange and needle cleaning effort obtained in Chapter Two.

Chapter 4

Simulations on Heterogeneity of Sharing Rate

Numerical simulation has become a useful part of mathematical modelling of infectious disease. Thus, computer simulations are taken here, using the package Berkeley Madonna version 8.3.18 (Macey & Oster, 2001) to assess the effects of heterogeneity between different groups of the population of drug users and different shooting galleries where the addicts share injecting equipment. Berkeley Madonna software was used to numerically solve the ordinary differential equations system of our models. The simulation results are conducted to estimate the impact of HCV during the time interval of 70 years (occasionally 100 years). The model parameters are estimated to produce HCV prevalence simulation results over time. In the this chapter, we assume that the model is homogeneous in shooting galleries which means that the addict groups share their needles in one shooting gallery ($q = 1$). We use this assumption for simplicity then we will discuss the heterogeneous cases of shooting galleries in Chapter Five. Under the assumption of homogeneity of shooting galleries, the

simulation results are performed to illustrate the prevalence of HCV among different groups of drug users. Alongside with our assumption of homogeneity of shooting galleries, we assume that the model parameters are all homogeneous except the needle sharing rates.

4.1 Sharing Rates in Glasgow Data Sets

Glasgow has one of the highest numbers of sharing injecting drug addicts in Europe with approximately 9,000 drug addicts (NESI, 2012). Our aim is to discuss the effect of heterogeneity on the prevalence of HCV in a population of drug users and shooting galleries. The data of the survey of drug users in Glasgow presents the rate of sharing borrowed needles that were previously used by another drug addict. To illustrate the prevalence of HCV among drug users in Glasgow, four different sets of data are applied to present the behaviour of the disease against time, with the first calculation of sharing rates using the data of sharing borrowed needles in 1990 and the second calculation of sharing rates using the data of sharing borrowed needles in 1993 where the disease takes off in both cases as the basic reproductive number $R_0 > 1$. These data give us that $R_0 > 1$, so to study the behaviour of the disease where $R_0 \leq 1$ we use the third set a hypothetical dataset which is related to the data of 1993. We expect that when $R_0 \leq 1$ the disease can die out. The three sets are obtained by using survey data collected by Health Protection Scotland, HPS, (Hutchinson et al., 2000). To compare the results for HCV spread with the results of Greenhalgh (1997) for HIV/AIDS amongst injecting drug users we use the fourth set of data which is collected by Goldberg et al., during the past six months amongst a sample of 503 injecting drug users in Glasgow in 1990 (Goldberg et al., 1996). To start our

simulation, we assume that the rest of the model parameters are homogeneous. Now, we will discuss the numerical estimations of these parameters.

4.2 Parameter Identification

In this section the numerical estimations of the parameters of the models are presented. Some of these parameter estimates are used in the model of Corson et al. (2012) and we also use them along with other parameters to study the effects of heterogeneity of HCV prevalence among different groups of addicts. Now we briefly discuss how the parameters are estimated.

4.2.1 Probability of Successful Needle Cleaning (ϕ_{ij})

The Harm Reduction Works website has a documentary (National Treatment Agency) presented by the research team who presented laboratory experiments on HIV and cleaning practices (NTA, 2009). This documentary suggests that cleaning needles and syringes with soaps, water or alcohol was successful in approximately 85% of needles, however cleaning them with water and bleach will kill all blood-borne infections in more than 99% of needles. Therefore it was assumed that the techniques used to successfully disinfect a needle and syringe contaminated with HIV will also disinfect one contaminated with HCV.

Corson et al. (2012) used survey data on addicts collected by HPS (Hutchinson et al. 2000) during the early 1990s to estimate needle cleaning probabilities. From a total of 2,058 addicts surveyed in Glasgow during 1990-1993, 1,379 reported that they had not injected with a used needle and syringe given, rented, or sold to

them by someone else in the previous six months. On the other hand, the majority (91%, 620/679) of the remaining 679 addicts reported that they always cleaned their needles before use, 24 mostly cleaned their needles before use, eight cleaned about half the time, 11 cleaned occasionally, 14 never cleaned and the remaining two said they did not know (Corson et al., 2012). Corson et al. estimate that 173 of 679 (25.5%) addicts who reported sharing needles and syringes would have cleaned their needles successfully the last time they injected, providing an estimate for ϕ_{ij} of 0.255 for group type i of addicts and shooting gallery j.

4.2.2 Needle Turnover Rate (τ_j)

A model by Kaplan and O'Keefe (1993) assumed that when there is no needle exchange present, the needles will circulate forever. However, this is not realistic as a needle has a limited working lifetime. On the other hand, Kaplan (1995) estimates that the natural working lifetime of a needle is 23.50 days resulting in a natural needle turnover rate of $\tau = 365/23.5 = 15.53$ per year (Kaplan & O'Keefe, 1993).

Corson et al. (2012) estimated that there were a total of 213,964 injecting events from a survey of 362 current addicts in the Greater Glasgow and Clyde area, generating an average of 591 injections per addicts per year. King et al. (2009) estimated that there were 7,918 addicts in the Glasgow area in 2003. Assuming that these 7,918 Glasgow addicts inject with needles at the same rate as those surveyed in 2007, then there were an estimated 4,679,538 injections in 2003. Corson et al. (2012) assumed that the distribution of needles was the same in 2003, they estimated that each needle was used approximately 4.46 times before it was exchanged. Moreover, they

assumed that addicts in 2003 inject on average at the same rate as those surveyed in 2007 (591 times per year), then addicts inject on average 1.62 times per day. Hence, if each needle is used approximately 4.46 times, with an average injection frequency of 1.62 per day then the working life of a single needle is approximately 2.75 days. This working life implies a total average needle turnover rate of 133 per year in each shooting gallery.

4.2.3 Duration of Acute HCV Infection ($1/\sigma$)

In their model, Vickerman et al. (2007) assumed that the duration of the acute phase ranges between six and 24 weeks in their modelling of HCV transmission in London. Two years after, Vickerman et al. (2009) estimated that the duration of the acute phase ranges from 3-24 months in their attempt to incorporate these individuals into their Pakistan HIV and HCV model. This estimation was used by Corson et al. (2012) and we use it in our simulation.

4.2.4 Rate that Addicts Leave the Population (μ)

Kaplan and O'Keefe (1993) estimate that the average incubation time of HIV is approximately ten years giving a rate for μ of 0.1 per addict per year. Greenhalgh and Hay (1997) use a value of $\mu = 0.25$ per addict per year in their modelling work on HIV in addicts. The authors assume that each addict will leave the population for non-HIV related reasons at rate 0.125 per year and each addict will also will leave the population due to AIDS related factors at rate 0.125 per year. Corson et al. (2012) assume that addicts will cease their sharing, injecting behaviour at the same rate in HCV models as they do in HIV models, provided that the HIV model estimate does

not incorporate disease specific factors. However, the authors estimated $\mu = 0.17$ addicts per year based on modelled estimates from Hutchinson et al. (2006) which applied to Glasgow addicts between 2000 and 2009 and accommodated mortality and cessation of injecting drug use.

4.2.5 Proportion of Addicts that Develop Immunity to HCV Re-infection (α)

This parameter is hard to estimate due to the large uncertainty associated with the level of immunity gained from previous infection with HCV. Some studies have modelled the disease considering the immune state. One of these is the model of Vickerman et al. (2007) which assumes that a proportion of addicts, ranging from 18% to 50%, are able to resolve their initial HCV infection and after a period of acute HCV infection all of these become immune for life. Later, Vickerman et al. (2009) assume that only a proportion of those that resolve their initial HCV infection go on to become immune with the remaining addicts becoming susceptible again. They estimate that the proportion of addicts who become immune ranges from 0 to 100%, for the reason that there is large uncertainty in estimating this parameter.

A fraction α (0.25) of the acutely infected addicts that did not spontaneously resolve HCV infection or leave the sharing injecting population developed immunity on resolving their HCV infection was assumed by Corson et al. (2012). According to some studies all of these addicts become immune for life (Micallef et al., 2006; Aitken et al., 2008).

4.2.6 Acute and Chronic Transmission Probabilities (α_h, α_y)

These are two of the biological parameters which were estimated by Corson et al. (2012). Their model was based on a model by Vickerman et al. (2007) who assumed a different probability for disease transmission for chronic and acute HCV while modelling the spread of HCV amongst addicts in London, UK. Initial transmission probability estimates for chronic HCV infection ranged from 0.84 - 10% with a multiplier factor for the transmission probability of HCV during the acute phase given by 1 - 10%. They used a numerical algorithm to determine possible model fits to London prevalence data. In their estimation Corson et al. (2012) consider the four best model fits which contained a transmission probability per sharing event in the chronic phase of either 4.1%, 1.8%, 4.3%, or 1.6%, with a factor increase during the acute phase of 1, 1, 1, and 2.7 respectively. This results in acute HCV transmission probability estimates of 4.1%, 1.8%, 4.3%, and 4.32% respectively.

4.2.7 Proportion of Addicts that Spontaneously Resolve HCV Infection (δ)

Hutchinson et al. (2006) assume that the rate of spontaneous resolution of acute HCV infections is in the range 15 - 40%, with a similar estimate of 18 - 50% used by Vickerman et al. (2007). In their simulation Corson et al. (2012) take $\delta = 0.26$, this was taken from a systematic review of longitudinal studies involving 675 subjects which suggests that 26% of individuals will spontaneously resolve their HCV infection (Micallef et al., 2006). This rate estimation also has been used in many recent studies, for example Vickerman et al. (2009) used it in their most recent modelling

work on HCV and HIV in Pakistan.

4.2.8 Rate of Sharing Needles and Syringes (λ_i)

The only heterogeneity parameter of our model in our simulation in this chapter is the sharing rate. Thus we will discuss this parameter in more detail and explain how to estimate the different rate for each different group in our simulation. For simplicity, many studies assumed homogeneous sharing rates although this is in contrast to what has been observed in the addict population (Kaplan & O'Keefe, 1993; Corson et al., 2012). In studies of HIV transmission amongst injecting drug addicts, Goldberg et al. (1996) assumed a mean shared injection rate for Glasgow addicts of 72.48 events per year. Later, Greenhalgh (1997) used the data from Goldberg et al. (1996) and restricting them to those addicts that share, gave an average number of shared injections $\lambda = 171$ per year. Corson et al. (2012) obtained λ from survey data of addicts from Glasgow during 1990-1993 and 2007, it was 103 per year.

In this simulation, we focus on the heterogeneity of the rate of sharing needles among addicts in different groups i, for $i = 1, 2, \ldots p$. Our aim is to discuss the effect of the heterogeneity on the prevalence of HCV in a population of drug users and shooting galleries. The data of a survey of drug users in Glasgow collected by HPS (Hutchinson et al., 2000) present the probability of sharing borrowed needles that were previously used by another drug addict. Table 4.1 shows these sharing rates of borrowed used needles which were collected by HPS during 1990 - 1993 detailing sharing over the past six months. In the attempt to compare a variety of sets of data in sharing needles rates, we also simulate data of sharing rates among drug users

in Glasgow collected by Goldberg et al. during the period of six months amongst a sample of 503 drug users in 1990 (Goldberg et al., 1996).

Frequency of Injecting	1990	1993
1-3 times per month	43	25
1 per day	7	4
1 per week	24	14
2-3 times per day	15	6
2-3 times per week	19	12
4 or more times per day	9	1
4-6 times per week	8	5
<1 per month	88	97
don't know	1	1
never	283	339

Table 4.1: The data from 1990 and 1993 of sharing of borrowed used needles taken from another addict in the previous six month period from a survey of drug users in Glasgow which was taken by HPS (Hutchinson et al. 2000).

Note that this questionnaire asks about the number of used needles borrowed from another addict in the last six months whereas in our model addicts borrow both exchanged unused needles and used needles. From scaling the rates in the table we can deduce the annual rate at which addicts in group i borrow used needles. We denote this by λ_i^*. However our model uses a different sharing rate. In our model λ_i denotes the annual rate at which those addicts in group i borrow both used and

unused needles. We shall now derive a formula which gives λ_i in terms of λ_i^*.

$\lambda_i^* = \lambda_i \times P$(a borrowed needle is a used needle rather than an exchanged needle).

But each needle is exchanged at rate τ and used by addicts at rate $\overline{\lambda}\gamma$ where

$$\overline{\lambda} = \frac{1}{n}\sum_{i=1}^{p} n_i \lambda_i,$$

is the average rate at which addicts share needles and $\gamma = n/m$. Hence

$$\lambda_i^* = \lambda_i \frac{\overline{\lambda}\gamma}{\overline{\lambda}\gamma + \tau}.$$

So writing

$$\overline{\lambda}^* = \frac{1}{n}\sum_{i=1}^{p} n_i \lambda_i^*,$$

$$\overline{\lambda}^* = \overline{\lambda}\frac{\overline{\lambda}\gamma}{\overline{\lambda}\gamma + \tau}.$$

Solving this equation for $\overline{\lambda}$ we deduce that:

$$\overline{\lambda} = \frac{1}{2}\left(\overline{\lambda}^* + \sqrt{\overline{\lambda}^{*2} + 4\overline{\lambda}^*\hat{\tau}}\right),$$

where $\hat{\tau} = \tau/\gamma$. In our model simulation, we calculate the sharing rates λ_i using the sharing rates λ_i^* of borrowed used needles which are found by the survey taken of addicts from Glasgow by HPS in 1990 and 1993 (Hutchinson et al. 2000). Tables 4.2 and 4.7 present these data and groups of addicts and their sharing rates in six different stages. We start with data from 1990, first we assume that the model is homogeneous. Then, we divide the addicts population into two groups according

to their sharing rates. This is followed by three groups with three different sharing rates, then five groups and five sharing rates. As we are interested in models with a greater number of groups because this may more accurately reflect the true degree of heterogeneity in the population, the population is then divided into seven groups with seven sharing rates and nine groups with nine sharing rates.

Later we display the simulation results of data from 1993, where we again divide the population into groups. First of all we assume that the model is homogeneous in the one group model. Then we separate the addicts population into two groups according to their sharing rates. This is followed by three groups with three different sharing rates, then four groups and four sharing rates. Then the population is divided into six groups with six sharing rates and nine groups with nine sharing rates.

4.3 Simulation Results using Data from 1990 (Hutchinson et al., 2000)

We start our simulation with different sharing rates of different groups using data from Glasgow drug users in 1990. The population size is made up of 9,000 drug addicts that mix heterogeneously. We first divide the population into groups and explore the behaviour of the disease in each different group. In the first group, we estimate the sharing rate λ in the whole population of drug users, it is found to be $\lambda = 167.39$ per year. This is followed by simulation for the two groups model where the first group consists of those who never share syringes ($\lambda_1 = 0$ per year), and the

rest of the drug users are in the second group. Table 4.2 illustrates the values of different sharing rates in each different group and the number of drug users.

Parameter	Definition	Estimate
ϕ_{ij}	Probability that an addict in group i cleans a needle in shooting gallery j before use, $i = 1, 2, ...9,\ j = 1.$	0.255
λ_i	Needle and syringe sharing rate in group i, $i = 1, 2, ...9.$	Tables 4.2, 4.7, and 4.12
τ_j	Needle turnover rate in shooting gallery $j,\ j = 1.$	133 per year
μ	Per capita rate at which addicts leave the sharing, injecting population.	0.17 per year
α_h	Acute HCV transmission probability.	0.0432
α_y	Chronic HCV transmission probability.	0.016
$1/\sigma$	Average duration of the acute stage.	0.5 years
δ	Proportion of acutely infected addicts who resolve HCV infection.	0.26
α	The proportion of those addicts spontaneously resolving HCV infection who become immune.	0.25
P_{ij}	The probability that an addict in group i chooses shooting gallery j to share a needle.	1
m_j	Number of needles in shooting gallery $j,\ j = 1.$	8,982

Table 4.3: Table of parameter estimates used in our simulations.

The results of the model simulation are presented to demonstrate the effect of heterogeneity of the prevalence of HCV among p groups of drug users. We calculated the model graphs using the above parameter values for the model for $p = 1, 2, 3, 5, 7$ and 9 and $q = 1$ shooting gallery. The group sizes and sharing rates for each group

One Group Model

λ	167.39
n	9,000

Two Group Model

λ_1	0.000	λ_2	388.2
n_1	5,135.08	n_2	3,864.91

Three Group Model

λ_1	0.000	λ_2	152.44	λ_3	1,440.25
n_1	5,135.08	n_2	3,157.25	n_3	707.66

Five Group Model

λ_1	0.000	λ_2	34.91	λ_3	364.75	λ_4	550.9	λ_5	1,996.09
n_1	5,135.08	n_2	2,032.25	n_3	1,125	n_4	272.18	n_5	435.48

Seven Group Model

λ_1	0.000	λ_2	34.91	λ_3	364.75	λ_4	462.67	λ_5	651.78	λ_6	1,629.46	λ_7	2,607.14
n_1	5,135.08	n_2	2,032.25	n_3	1,125	n_4	145.16	n_5	127.01	n_6	272.17	n_7	163.3

Nine Group Model

λ_1	0.000	λ_2	19.55	λ_3	91.25	λ_4	231.43	λ_5	423.66	λ_6	462.67	λ_7	651.78	λ_8	1,629.46	λ_9	2,607.14
n_1	5,135.08	n_2	1,596.77	n_3	435.48	n_4	344.75	n_5	780.24	n_6	145.16	n_7	127.01	n_8	272.17	n_9	163.3

Table 4.2: Sharing needles and syringes rates λ_i, sizes of group n_i of drug users for $i = 1, 2, ..., 9$ using data from 1990.

were taken as mentioned earlier from a survey of addicts in Glasgow in 1990, where the rest of the model parameter estimates are taken from the model by Corson et al. (2012). Table 4.3 shows the set of parameter estimations and their definitions.

As $j = 1$ we assume that every addict in group i will choose a needle in shooting gallery j, so $P_{ij} = 1$ for simplicity in this stage of discussion. Moreover, the number of addicts in Glasgow was taken as $n = 9,000$, and the number of needles is estimated to be $m = 8,932.03$. The figure for the number of needles is taken from the model of Corson et al. (2012) who take $\gamma = 1.002$ as the ratio of addicts to needles (Griesbach et al., 2006; King et al., 2009). Then we estimate Λ_{ij}, the arrival rate of a single addict in group i at a needle in shooting gallery j:

$$\Lambda_{ij} = \frac{\lambda_i n_i}{m_j} \qquad\qquad i = 1, 2, ...9, \quad j = 1.$$

4.3.1 Estimation of the Basic Reproductive Number (R_0)

The estimation of reproductive numbers is typically an indirect process because some of the parameters on which these numbers depend are difficult, if not impossible, to quantify directly. This parameter determines a threshold: whenever $R_0 > 1$, a typical infective gives rise, on average, to more than one secondary infection, leading to an epidemic. In order to explore the disease behaviour we need to estimate this threshold. We estimate R_0 using Table 4.3 and Table 4.2 and our expression of this number, which is:

$$R_0 = \xi \frac{\sum_{k=1}^{p} \lambda_k^2 n_k (1 - \phi)}{m\Big(\sum_{l=1}^{p} \frac{\lambda_l n_l}{m} + \tau \Big)}, \tag{4.1}$$

where $\xi = (\alpha_y\sigma(1-\delta) + \alpha_h\mu)/\mu(\mu+\sigma)$ as given in equation (2.22). In each stage of our simulation, we estimate R_0 using the sharing rates in the different groups.

Now we present the simulation results of each model. In each model simulation we calculate R_0, and equilibrium solutions for both addicts and needles. The overall proportions of infectious addicts, needles and HCV antibody positive addicts are plotted against time for seventy years. Table 4.4 summaries these results for all the six models.

Model	R_0	Infectious addicts	Infectious needles	Antibody positive
One group	5.8	76%	42%	85%
Two group	13.5	36%	47%	40%
Three group	35	34%	48%	37%
Five group	45.7	28%	48%	32%
Seven group	48.11	28%	48%	32%
Nine group	48.3	27%	48%	30%

Table 4.4: Comparing the six models in the basic reproductive number and equilibrium percentage of proportion of infectious addicts, needles and antibody positive addicts using data from 1990.

Note that the values of R_0 calculated are much higher than those normally observed for homogeneous models. However, the interpretation of R_0 is different for models with heterogeneity so this does not necessarily indicate a problem with these values. The simulation results present in Table 4.4 indicate that as the number of group increases, R_0 values increases too and the overall prevalence of HCV among addicts decreases. The increasing of the value of R_0 because we take the average value of all R_0's for all groups so as the number of groups increased the number of

R_0's increased too. This is because as we have differen groups with different values of sharing rates according to this we have more R_0's according to each group of addicts. Moreover, there is a large amount of addicts whom never share needles, which implies a large number of non-infected addicts comparing with a small amount of addicts who highly sharing needles, which implies that these small number of addicts will be infected (see table 4.2). Thus, we have the overall of proportion of infectious addicts and antibody positive addicts come down, as in the most heterogeneity models (for example the nine group model) there are groups of addicts can not be reached.

4.3.2 One Group Model

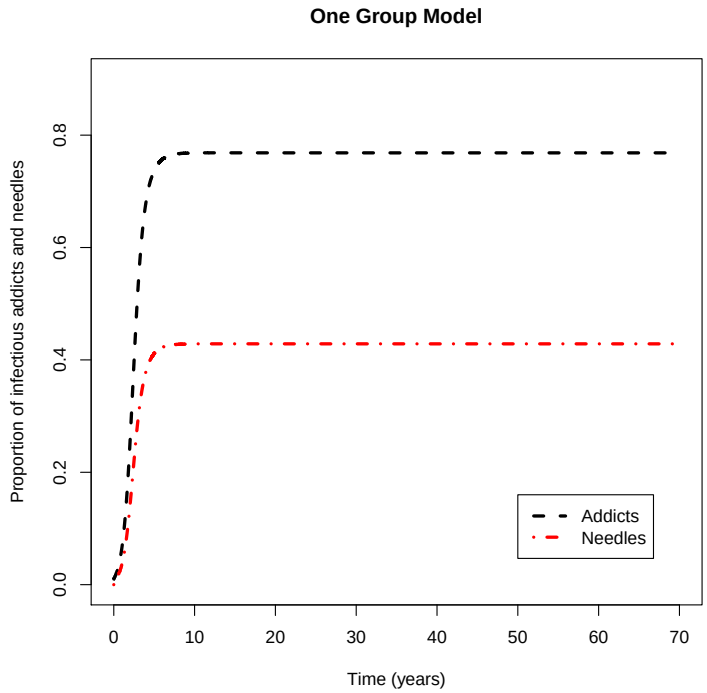


Figure 4.1: The proportions of addicts and needles in Glasgow when $R_0 = 5.8$ in the one group model using data from 1990.

A simulation is performed for HCV prevalence for $p = q = 1$. Using the set of

parameters given in Table 4.3 we estimate that $R_0 = 5.8 > 1$. We assume that at time $t = 0$, $\pi_{x1}(0) = 0.99$ (so 99% of addicts were not infected with HCV), $\pi_{x_1 1}(0) = 0$, $\pi_{h_1 1}(0) = 0.01$ (so 1% of addicts were in the acute h_1 stage) and $\pi_{h_2 1}(0) = \pi_{y1}(0) = \pi_{z1}(0) = 0$. Similarly, for the fractions of infectious needles at time $t = 0$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = 0$ (so no needles are infected with HCV). One of the most important aspects of disease modelling is the number of infectious addicts at any given time, therefore the fraction of infected addicts $(\pi_{h_1 1} + \pi_{h_2 1} + \pi_{y1})$ against time is displayed in Figure 4.1. We notice that the fraction of needles and addicts infected with the disease reaches a steady endemic states. The long-term prevalence of HCV in addicts is over 70% as can be seen in Figure 4.1. The estimated steady state values are $(\pi^*_{x1}, \pi^*_{x_1 1}\pi^*_{h_1 1}, \pi^*_{h_2 1}, \pi^*_{y1}, \pi^*_{z1}) = (0.1447, 0.0262, 0.0585, 0.0205, 0.6893, 0.0605)$. For needles at each stage of infectivity $(\beta^*_{h_1 1}, \beta^*_{h_2 1}, \beta^*_{y1}) = (0.0326, 0.0114, 0.3844)$. These values are consistent with formulae for equilibrium values given in equations (3.1) - (3.4) if the relevant parameters values are substituted.

4.3.3 Two Group Model

The central aim of this model is to study the effect of heterogeneity on the spread of HCV amongst addicts. Thus, we divide the population of addicts into two main groups. One group is addicts who never share needles and syringes and the other group is addicts who are sharing injecting equipment. We can see from Figure 4.2 that although this sharing rate is higher than the sharing rate in the homogeneous case, we notice that the overall long-term equilibrium infectious proportion of HCV infected addicts in Glasgow is lower than in the homogeneous case. This is because we take the average of prevalence for both groups, first who never share which has

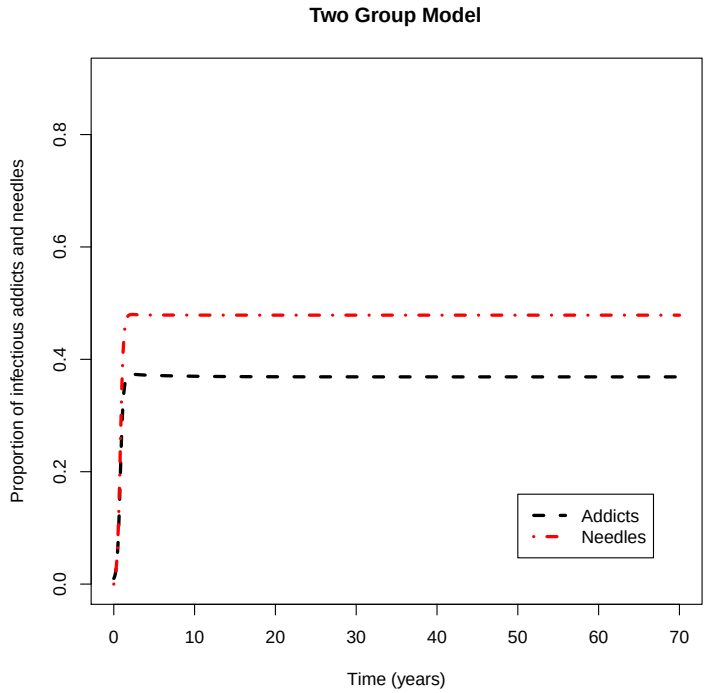


Figure 4.2: The proportions of addicts and needles in Glasgow when $R_0 = 13.5$ in the two group model using data from 1990.

the largest number of addict (non-infected) and second group who sharing with lower number of addicts (infected). As initial proportions of infection we assume that at time $t = 0$, for $i = 1, 2$, $\pi_{xi}(0) = 0.99$ (so in each group 99% of addicts were not infected with HCV), $\pi_{h_1 i}(0) = 0.01$ and $\pi_{x_1 i}(0) = \pi_{h_2 i}(0) = \pi_{yi}(0) = \pi_{zi}(0) = 0$. Similarly, for infectious needle fractions at time $t = 0$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = 0$ (so no needles are infected with HCV). R_0 was estimated to be 13.5 using the set of parameters in Table 4.3 and the formula (4.1). We can see that the disease reaches a steady endemic solution. The overall estimated steady state values are $(\pi_x^*, \pi_{x_1}^* \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.5969, 0.0053, 0.0281, 0.0098, 0.3306, 0.0290)$. For p

groups of addicts, these are calculated using the following formula:

$$\pi_s^* = \frac{\sum_{i=1}^{p} n_i \times \pi_{si}^*}{\sum_{i=1}^{p} n_i}, \qquad s = x, x_1, h_1, h_2, y, z, \quad p = 2.$$

For needles in each state of infectivity, we deduce that the approximate steady state values are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0.0364, 0.0128, 0.4287)$.

4.3.4 Three Group Model

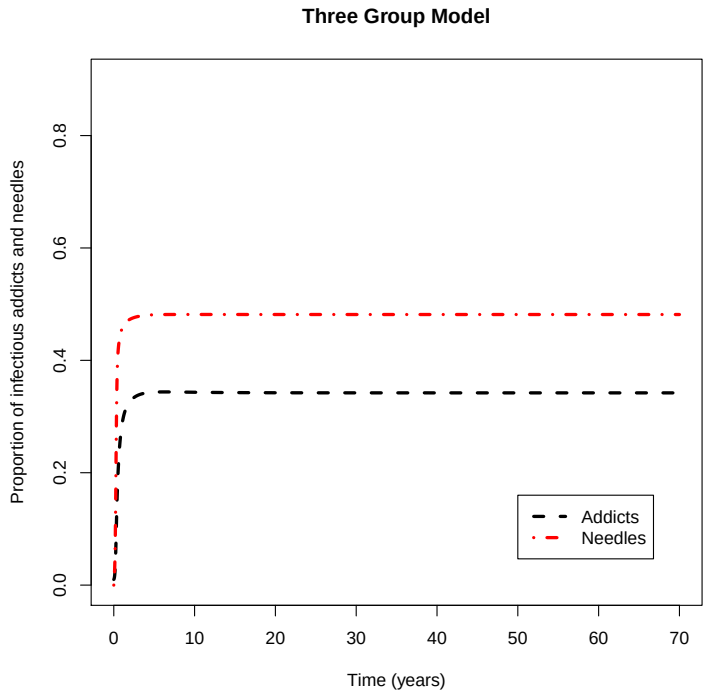


Figure 4.3: The proportions of addicts and needles in Glasgow when $R_0 = 35$ in the three group model using data from 1990.

The simulation in this stage includes three groups of addicts $p = 1, 2$ and 3, where one group consists of addicts who never share needles $\lambda_1 = 0$ per year, the second group consists of addicts sharing needles at a low rate where $\lambda_2 = 152.44$ per year and the third group consists of addicts who share needles at a high rate $\lambda_3 = 1,440.25$

per year. We calculate $R_0 = 35 > 1$. At time $t = 0$ for $i = 1, 2, 3$, $\pi_{xi}(0) = 0.99$, $\pi_{x_1 i}(0) = 0$, $\pi_{h_1 i}(0) = 0.01$ $\pi_{h_2 i}(0) = \pi_{yi}(0) = \pi_{zi}(0) = 0$. Similarly, for infectious needle fractions at time $t = 0$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = 0$. Figure 4.3 shows that the overall equilibrium prevalence of HCV in needles and syringes is higher than the prevalence of HCV among addicts. Moreover, we can see that the overall equilibrium prevalence of HCV amongst addicts is lower in the three groups model than in the one group model and the two groups model. In the three groups model the overall equilibrium prevalence is about 28% and it is achieved after around ten years. The overall average equilibrium prevalence in addicts is $(\pi_x^*, \pi_{x_1}^* \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.6217, 0.0094, 0.0260, 0.0091, 0.3067, 0.0269)$. For needles at each stage of infectivity, we deduce that the approximate steady state values are $(\beta_{h_1 1}^*, \beta_{h_2 1}^*, \beta_{y1}^*) = (0.0366, 0.0128, 0.4314)$. Moreover, we simulated the four group model where the results are not displayed, as the behaviour of the four group model and the three group model are very similar.

4.3.5 Five Group Model

To illustrate the heterogeneity effects in the spread of HCV, we discuss and frame a five groups model where the five groups have different sharing rates λ_i for $i = 1, 2, 3, 4, 5$. We set the groups according to their sharing rate where the first group has the lowest rate $\lambda_1 = 0.0$ per year and group five has the highest rate with $\lambda_5 = 1,996.09$ per year. Figure 4.4 presents the behaviour of HCV in the heterogeneously mixing groups. As mentioned earlier, based on the parameters in Table 4.3, an estimation of the basic reproductive number is made, $R_0 = 45.7 > 1$. Furthermore, we are assuming that at time $t = 0$, $\pi_{xi}(0) = 0.99$ $\pi_{x_1 i}(0) = 0$, $\pi_{h_1 i}(0) = 0.01$,

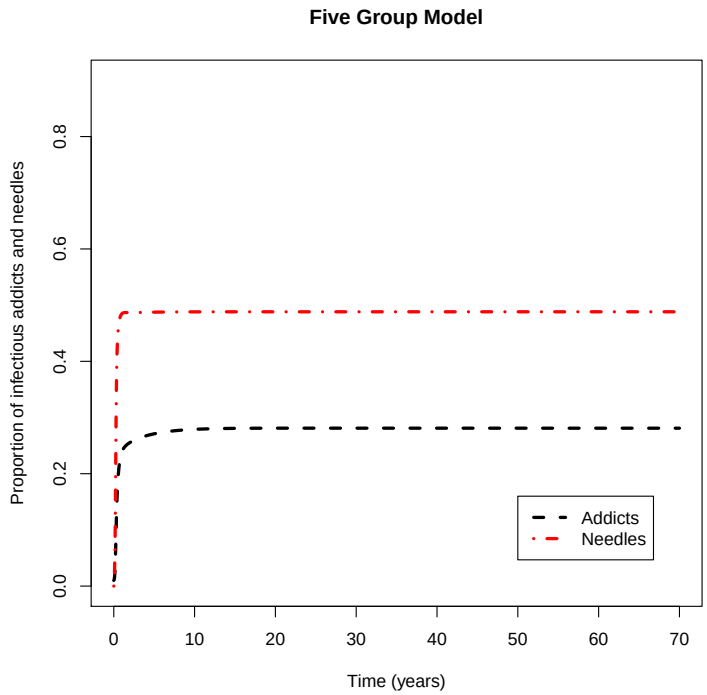


Figure 4.4: The proportions of addicts and needles in Glasgow when $R_0 = 45.7$ in the five group model using data from 1990.

and $\pi_{h_2 i}(0) = \pi_{yi}(0) = \pi_{zi}(0) = 0$ for all i. Similarly, for infectious needle fractions at time $t = 0$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = 0$. We notice that the fraction of addicts and needles infected with the disease reach a steady endemic solution. The estimated steady state values for addicts are $(\pi_x^*, \pi_{x_1}^* \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.6745, 0.0130, 0.0221, 0.0077, 0.2597, 0.0228)$. For needles at each stage of infectivity, we deduce that the approximate steady state values are $(\beta_{h_1 1}^*,\ \beta_{h_2 1}^*, \beta_{y1}^*)= (0.0371, 0.0130, 0.4365)$. Moreover, we simulated the six group model where the results are not displayed, as the behaviour of the six group model and the five group model are very similar.

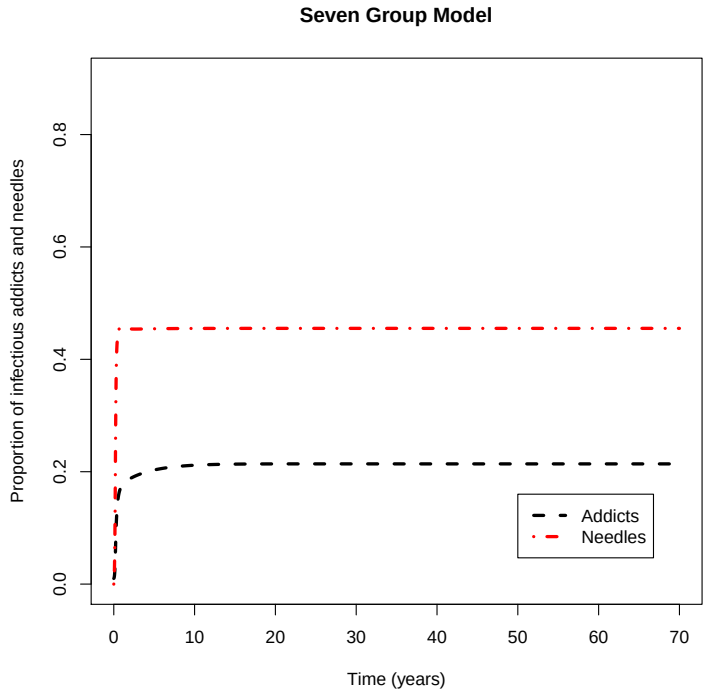


Figure 4.5: The total infected proportions of addicts and needles in Glasgow when $R_0 = 48.11$ in the seven group model using data from 1990.

4.3.6 Seven Group Model

We can see that the prevalence of HCV may decrease with the increasing of the number of groups in each different model. Now we present a simulation for $p = 7$, along with seven different sharing rates λ_i for $i = 1, 2, 3, 4, 5, 6, 7$. These groups are arranged according to their sharing where the first group has the lowest $\lambda_1 = 0.0$ per year and the seventh group has the highest where $\lambda_7 = 2,607.14$ per year. In this simulation we follow similar initial proportions for the model variable as previously, then we find that $R_0 = 48.11 > 1$ which leads us to believe that the disease will persist in this model. Figure 4.5 displays the model equilibrium prevalence with the overall steady state equilibrium prevalence in addicts being $(\pi_x^*, \pi_{x_1}^* \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.6746, 0.0130, 0.0220, 0.0077, 0.2596, 0.0228)$. Needles steady states values are $(\beta_{h_1 1}^*,$

$\beta^*_{h2}1, \beta^*_{y1}$)=(0.0371, 0.0130, 0.4365).

4.3.7 Nine Group Model

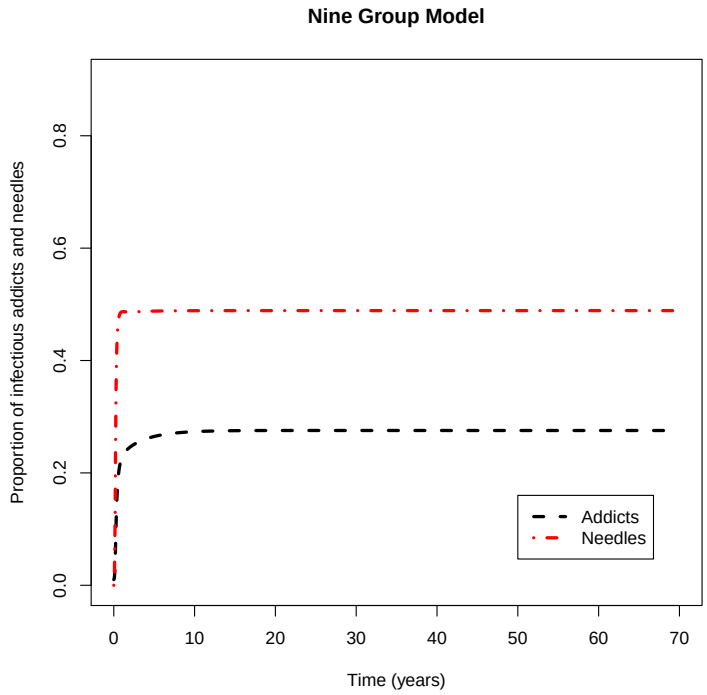


Figure 4.6: The proportions of addicts and needles in Glasgow when $R_0 = 48.3$ in the nine group model using data from 1990.

A simulation for nine groups of drug addicts was performed to predict the behaviour of the disease. Figure 4.6 emphasises the fact that in the nine group model the overall long-term prevalence of HCV is the lowest comparing with other models including the homogeneous model. As we mention this because a large number of addicts in this model never share needle which implies large number of non-infected addicts and a small number of infected addicts whom are sharing needles at high rate, thus the overall average of HCV precleaned among addicts in this model is the lowest. Nine groups of addicts are included and one shooting gallery. As in previous

simulations we start at time $t = 0$ for $i = 1, 2, \ldots, 9$, $\pi_{xi}(0) = 0.99$ $\pi_{x_1 i}(0) = 0$, $\pi_{h_1 i}(0) = 0.01$ $\pi_{h_2 i}(0) = \pi_{yi}(0) = \pi_{zi}(0) = 0$ also, for infectious needle fractions at time $t = 0$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = 0$. We also use the parameter estimation presented in Table 4.3 to calculate $R_0 = 48.3 > 1$.

We clearly can see from Figure 4.6 that after nearly ten years the total proportion of infectious addicts reaches a steady equilibrium state with the following values $(\pi_x^*, \pi_{x_1}^* \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.6907, 0.0123, 0.0209, 0.0073, 0.2468, 0.0216)$. For needles in each stage of infectivity, we deduce that the approximate steady state values are $(\beta_{h_1 1}^*, \beta_{h_2 1}^*, \beta_{y1}^*)$=$(0.0372, 0.0130, 0.4379)$.

4.4 Comparison of Models with Different Numbers of Groups

4.4.1 Infectious Addicts

We aim to incorporate the total proportions of infected addicts for all six models. Figure 4.7 shows the plots of these proportions of infected addicts in Glasgow using data from 1990 (Hutchinson et al., 2000). Clearly, we can see the highest equilibrium proportion of infectious addicts happened in the one group model (homogeneous model) where it is nearly 76%, whilst the nine group model (heterogeneity model) has the lowest overall average of equilibrium prevalence of 27%. This indicates that for this observed data increasing the heterogeneity of the addicts population may reduce the overall endemic equilibrium level of disease amongst addicts. The reason for this is that the observed distribution of needle sharing rates is very skew. As the

heterogeneity increases the prevalences in the smaller groups gets higher and in the larger groups lower so the overall endemic prevalence decreases.

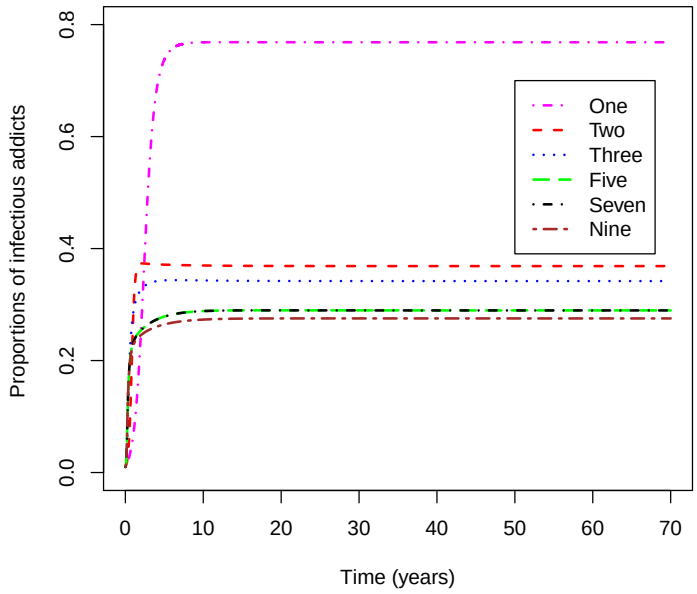


Figure 4.7: The total proportion of infectious addicts in all models in Glasgow using data from 1990.

Moreover, the behaviour of infectious addicts in the five and seven group models in Figure 4.7 shows that these models behave similarly, also this can be seen from the the total proportion of infectious addicts in Table 4.4. As the number of groups increases the initial speed of increase of the epidemic (which is related to R_0) increases. So our simulations are consistent with our theoretical results which show that in this situation the homogeneous model has the lowest value of R_0. Table 4.4 presents the basic reproductive number for each model and we can see that the seven and nine group models have the highest numbers for R_0.

Moreover, Table 4.5 compares the number of groups and the endemic equilibrium

prevalence values in each stage: susceptible, acute, chronic and immune. Therefore, we can see that as the number of groups increases the endemic equilibrium prevalence of infectious addicts decreases. This indicates that increasing the heterogeneity in the addicts population may reduce the long term endemic equilibrium proportion of HCV among this population.

We also did simulations for the four group model (where results are not presented), we found that the results for four, five, seven and nine group models were very close.

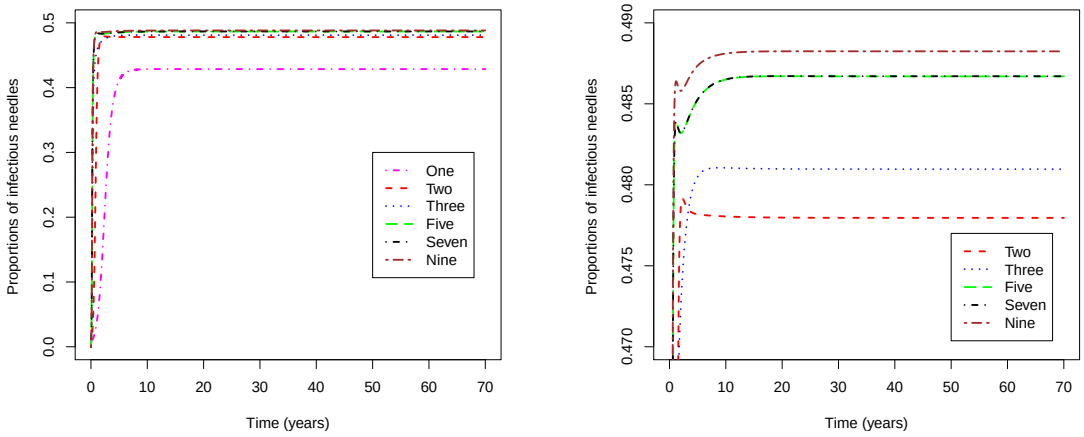
Models	π_x^*	$\pi_{x_1}^*$	$\pi_{h_1}^*$	$\pi_{h_2}^*$	π_y^*	π_z^*
One group	0.1447	0.0262	0.0585	0.0205	0.6892	0.0326
Two group	0.5969	0.0053	0.0281	0.0098	0.3306	0.0290
Three group	0.6217	0.0093	0.0260	0.0091	0.3067	0.0269
Five group	0.6745	0.0130	0.0220	0.0077	0.2597	0.0228
Seven group	0.6746	0.0130	0.0220	0.0077	0.2596	0.0228
Nine group	0.6907	0.0123	0.0209	0.0073	0.2468	0.0216

Table 4.5: Comparing the endemic equilibrium proportions of infectious addicts for all six models using data from 1990.

4.4.2 Infectious Needles

We have assumed that the all addicts groups are sharing needles and syringes in one shooting gallery, Figure 4.8 shows the total proportions of infectious needles and syringes in this shooting gallery in all six models with different numbers of addicts. Again we note that the more groups there are, the greater the degree of heterogeneity, the bigger R_0 is, and the faster the disease initially takes off. However,

when we consider the equilibrium prevalence we find that in contrast to the total proportion of infectious addicts, the one group model has highest endemic equilibrium proportion of infectious needles and infectious addicts. Table 4.6 displays the endemic equilibrium proportions of needles for all the models.



(a) The total proportion of infected needles in all models in Glasgow using data from 1990.

(b) Clarification of the curves of models two, three, five, seven and nine where the y axis is (0.47, 0.49).

Figure 4.8: Infectious needles proportion.

Models	$\beta^*_{h_1}$	$\beta^*_{h_2}$	β^*_y
One group	0.0326	0.0114	0.3844
Two group	0.0364	0.0128	0.4287
Three group	0.0366	0.0128	0.4314
Five group	0.0371	0.0130	0.4365
Seven group	0.0371	0.0130	0.4365
Nine group	0.0372	0.0130	0.4379

Table 4.6: Comparing the endemic equilibrium proportions of infectious needles for all six models using data from 1990.

As the number of groups increases the model becomes increasingly heterogeneous and in general the endemic equilibrium proportion of infectious needles increases. However, note that this endemic equilibrium proportion is similar for the five, seven and nine group models. Again we found that the four group model (not presented) is similar to the three group model. Also, the endemic equilibrium proportions of the four, five, seven and nine group models are very similar, and we can see this clearly from Table 4.6 and Figure 4.8.

4.4.3 Antibody Positive Addicts

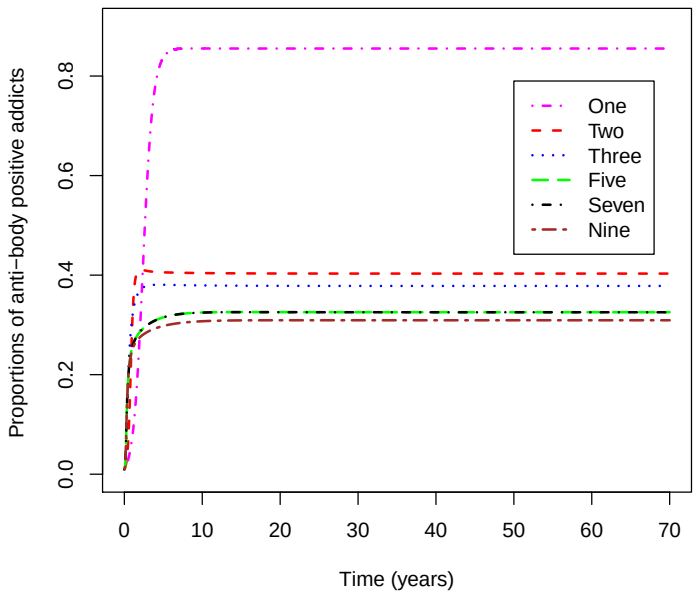


Figure 4.9: The total proportion of antibody positive addicts in all models in Glasgow using data from 1990.

As HPS collects data on HCV antibody positive addicts it is useful to consider the total proportion of HCV antibody positive addicts against time. In our model the antibody positive classes are the resolved susceptibles $\pi_{x_1 i}$, acutely infected $\pi_{h_1 i}$

and $\pi_{h_2 i}$, chronically infected π_{yi} and immune π_{zi} for $i = 1, 2, \ldots, p$. The results are displayed in Figure 4.9. We see that the pattern is similar to the total proportion of infected addicts. The disease takes off fastest in the most heterogeneous models but the endemic equilibrium proportion antibody positive is lowest in the more heterogeneous models. Moreover, it is clear that the five, seven and nine group models display very similar behaviour. Again, we simulate the antibody positive addicts in the four group model where the graph is not presented, we found that this model behaves similarly to the five and seven group models.

4.5 Simulation Results Using Data of 1993 (Hutchinson et al., 2000)

The survey of sharing borrowed needles from other addicts in the period of six months in Glasgow in 1993 that yields λ_i^* (Hutchinson et al., 2000) was used to calculate the total sharing needles rates λ_i. There seems to have been a substantial drop in the level of self-reported sharing amongst injecting intravenous drug users in Glasgow between 1990 and 1993 (Hutchinson et al., 2000). Data on sharing rates in 1993 were used to investigate the effect of this drop. We use the same formula that have been used for the data in 1990, to calculate the sharing rates λ_i for $i = 1, 2, \ldots p$. We find that in both sets of data, the basic reproductive numbers are above one, thus the solution will approach the endemic equilibrium over seventy years.

We will briefly discuss and present some graphs of the plots of the models. Table 4.7 presents the sharing rates for each group in the five different models. As before we

One Group Model

λ	92.36
n	9,000

Two Group Model

λ_1	0.000	λ_2	283.27
n_1	6,065.6	n_2	2,934.4

Three Group Model

λ_1	0.000	λ_2	153.4	λ_3	1484.45
n_1	6,065.61	n_2	2,648.11	n_3	286.28

Four Group Model

λ_1	0.000	λ_2	39.24	λ_3	495.92	λ_4	1,484.45
n_1	6,065.61	n_2	1986.08	n_3	662.02	n_4	286.26

Nine Group Model

λ_1	0.000	λ_2	26.83	λ_3	125.24	λ_4	317.64	λ_5	581.49	λ_6	635.04	λ_7	894.60	λ_8	2,236.57	λ_9	3,578.4
n_1	6,065.61	n_2	1,735.58	n_3	250.49	n_4	214.71	n_5	447.31	n_6	89.46	n_7	71.57	n_8	107.35	n_9	17.89

Table 4.7: Sharing needles and syringes rates λ_i, sizes of group n_i of drug users for $i = 1, 2, ..., 9$ using data from 1993.

assume initially that 1% of addicts are in the acute infectious h_1 class, the remaining 99% are in the susceptible x class and no needles are infected. First we consider the homogeneous case where $p = q = 1$, the sharing rate is 94.34 per year. Then we divide the population into two groups, one for those who never share needles and the second group who share needles. This is followed by the three and four group models where they behave similarly to each other as can be seen from Figure 4.10. Finally, the most heterogeneity model with nine group with nine different sharing rates. These five models are shown in Figure 4.10, which display the overall of prevalence of HCV in addicts and needles in each model. It can be seen, as the number of groups increases the initial speed of increase of the epidemic (which is related to R_0) increases. So our simulations are consistent with our theoretical results which show that in this situation the homogeneous model has the lowest value of R_0.

Models	R_0	Infectious addicts	Infectious needles	Antibody positive addicts
One group	2.37	53%	22%	62%
Two group	7.28	26%	32%	28%
Three group	21.43	24%	33%	26%
Four group	24.64	18%	34%	21%
Nine group	32.08	17%	34%	20%

Table 4.8: Comparing the five models in the basic reproductive number and equilibrium of proportion of infectious addicts, needles and antibody positive addicts using data from 1993.

Table 4.8 presents the basic reproductive number for each model, percentage of proportion of infectious addicts, needles and antibody positive addicts. We simulate

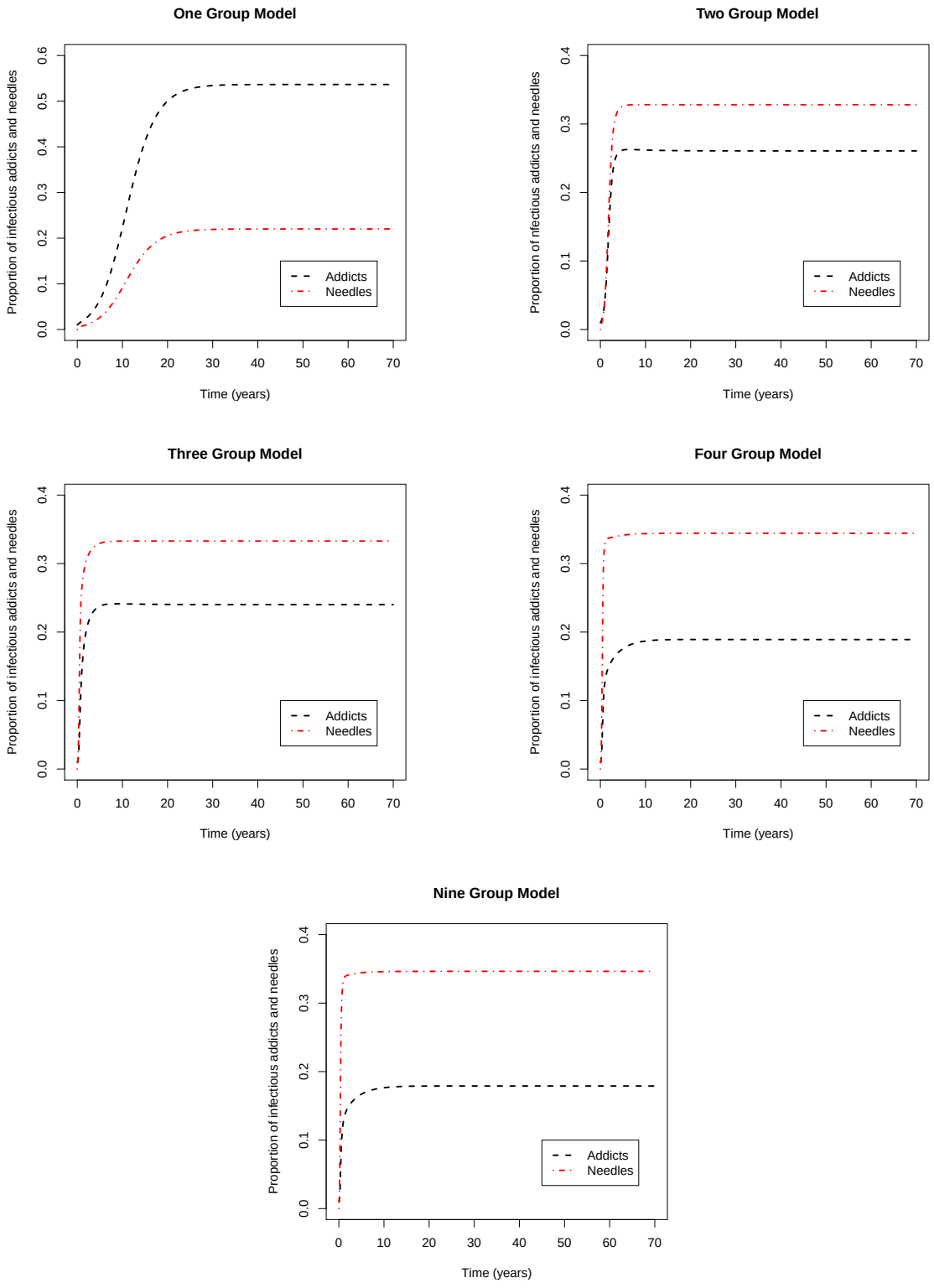


Figure 4.10: The total proportions of infectious addicts and needles in Glasgow in the five models using data from 1993.

the five and the six group models (which are not presented), these models behave similarly to the four group model. The nine group model has the highest value of R_0 and the lowest equilibrium proportions of infectious addicts, needles and antibody positive addicts. Although the data set of 1993 is different than data set of 1990, we notice the results are similar as $R_0 > 1$ in both cases. Also, the biological interpretation of heterogeneity on the HCV spread that heterogeneity may reduce the overall proportions of infectious of HCV among addicts population although the value of R_0 is high (as we explained earlier the reason of increasing in R_0 values with the increasing of the number of groups).

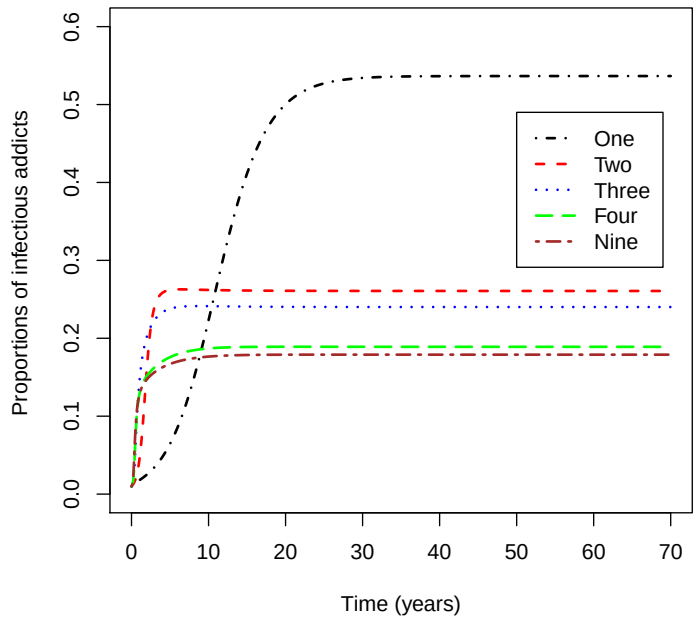


Figure 4.11: Comparing all the proportions of infectious addicts for all models in Glasgow using data from 1993.

4.6 Comparison of Models with Different Numbers of Groups

4.6.1 Infectious Addicts

To compare the behaviour of all five models, we present the plots of the proportions of infectious addicts against time. Figure 4.11 shows the effects of heterogeneity of the prevalence of HCV among drug addicts. We can see that the one group model has the highest rate of infectious addicts whereas the nine group model has the lowest. Clearly, it appears from Figure 4.11 that after about ten years the fraction of addicts and needles infected with the disease reach steady endemic solutions. The overall average endemic equilibrium prevalence in addicts is presented in Table 4.9 and the overall average endemic equilibrium prevalence in needles is presented in Table 4.10. For the one group model this endemic equilibrium is reached after about twenty years.

Models	π_x^*	$\pi_{x_1}^*$	$\pi_{h_1}^*$	$\pi_{h_2}^*$	π_y^*	π_z^*
One group	0.3737	0.0474	0.0409	0.0143	0.4812	0.0422
Two group	0.7117	0.0071	0.0198	0.0068	0.2338	0.0205
Three group	0.7312	0.0097	0.0183	0.0064	0.2153	0.0189
Four group	0.7840	0.0120	0.0144	0.0050	0.1695	0.0148
Nine group	0.7954	0.0114	0.0136	0.0047	0.1605	0.0140

Table 4.9: Comparing the endemic equilibrium proportions of infectious addicts for all five models using data from 1993.

4.6.2 Infectious Needles

Note that although we consider one shooting gallery where all the groups of drug users share the needles and syringes, there is a significant difference between the prevalence of HCV in the needles. Figure 4.12 illustrates that two group model has the highest proportion of infectious needles which is nearly 23%. On the other hand, the one group model has a lower equilibrium proportion of infectious needles than the two group model. Also, Figure 4.20 shows that the behaviour of the three and four group models are indistinguishable, also we can say the same about the behaviour of the six and nine group models. Table 4.10 displays the endemic equilibrium solutions of the five different models in the h_1, h_2 acute stage and y chronic stage. From this table we can see that as the number of groups of the models increases, the endemic equilibrium solutions decrease for all six models.

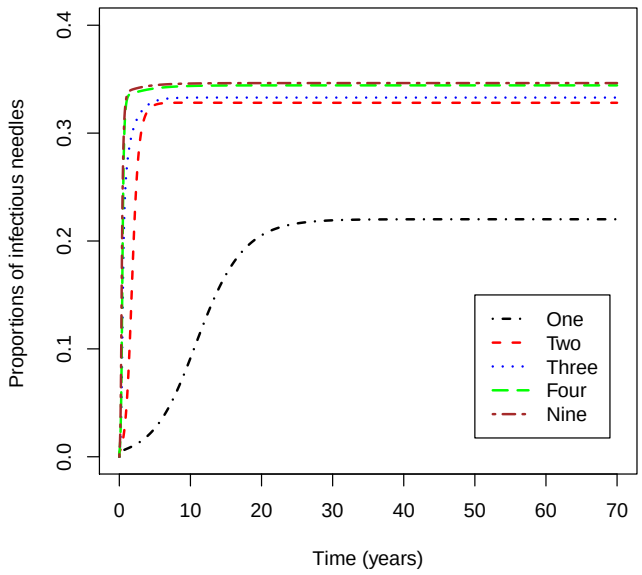


Figure 4.12: Comparing all the proportions of infectious needles for all models in Glasgow using data from 1993.

Models	$\beta^*_{h_1}$	$\beta^*_{h_2}$	β^*_y
One group	0.0167	0.0058	0.1974
Two group	0.0250	0.0087	0.2943
Three group	0.0253	0.0089	0.2986
Four group	0.0262	0.0092	0.3087
Nine group	0.0264	0.0092	0.3106

Table 4.10: Comparing the endemic equilibrium proportions of infectious needles for all five models using data from 1993.

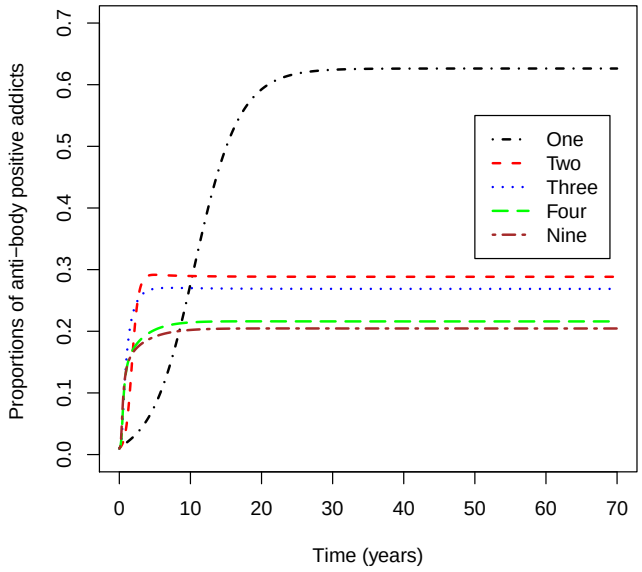


Figure 4.13: Comparing all the proportions of antibody positive addicts for all models in Glasgow using data from 1993.

4.6.3 Antibody Positive Addicts

Table 4.8 displays the equilibrium proportion of the antibody positive addicts in our simulations for data from 1993. As for earlier simulations, the antibody positive

classes are the susceptible x_{1i}, acutely infected h_{1i} and h_{2i}, chronically infected y_i and immune z_i for $i = 1, 2, ..., p$. The results are displayed in Figure 4.13, where we can see that the models with lower number of groups (the more homogeneous models), have the highest proportion of antibody positive addicts. Again, the pattern is similar to the total proportion of infected addicts using data from 1993.

4.7 Simulation Results using Data from 1990 (Goldberg et al., 1996)

Now we present the simulation results using data of sharing rates among drug users in Glasgow collected by Goldberg et al., during the past six months amongst a sample of 503 injecting drug users in Glasgow in 1990 (Goldberg et al., 1996). We scale the size of the sample to the currently number of injecting drug users in Glasgow (which is 9,000). These data were used without adjustment by Greenhalgh (1997) in his model of the spread of HIV/AIDS among injecting drug users. It would be more realistic to adjust these sharing rates for the effect of needle exchange in the same way as for the above datasets which were collected by HPS in 1990 and 1993. However to obtain a broad spectrum of simulated situations and to compare the results for hepatitis C with the results of Greenhalgh (1997) for HIV/AIDS amongst injecting drug users we use unadjusted rates.

Table 4.11 displays the five models where addicts are sharing needles in one shooting gallery. Similar initial conditions are used by assuming initially that 1% of addicts are in the acute infectious h_1 class, the remaining 99% are in the susceptible x

class and no needles are infected. In the homogeneous model where $p = q = 1$ we find that the sharing rate is $\lambda = 72.48$ per year. This give us that $R_0 = 1.6 > 1$, thus we expect the disease will take off in both addicts and needles. After nearly 30 years we can see from Figure 4.14 (first left plot), the model achieves a steady equilibrium solution with the following values $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*)$ =(0.5774,0.0475,0.0265,0.0093, 0.3117, 0.0273). The steady equilibrium solutions for the needles are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) =$ (0.0093, 0.0032, 0.1101). To investigate the impact of heterogeneity we divide the addicts' population into different groups and study the behaviour of HCV in both addicts classes and needles. Next, we take the two group model where the first group consists of those who never share, $\lambda_1 = 0$ per year, and the second group has $\lambda_2 = 171.1$ per year. We find $R_0 = 3.7 > 1$ and the equilibrium total proportion of infectious addicts is nearly 28% and of infectious needles is nearly 24%. The model reaches equilibrium steady state after about 10 years. More models are discussed later, we consider the three group model where the sharing rates are presented in Table 4.11, we find that $R_0 = 9 > 1$ and the equilibrium total proportion of infectious addicts is nearly 17% and of infectious needles is nearly 28%. Then, we simulate the four group model with four different sharing rates (see Table 4.11). $R_0 = 15 > 1$ and the equilibrium total proportion of infectious addicts is nearly 16% and of infectious needles is nearly 28%.

Moreover, we attempt to simulate five, six and seven group models, we find these models behave very similarly to the four group model thus we did not present them here. As R_0 is increasing with an increasing of the number of groups in models, we compute R_0 in the nine group model and find it to be 22.37. Also, this model has

One Group Model

λ	72.48
n	9,000

Two Group Model

λ_1	0.000	λ_2	171.1
n_1	5,188.87	n_2	3,811.13

Three Group Model

λ_1	0.000	λ_2	12.04	λ_3	425.4
n_1	5,188.87	n_2	2,343.94	n_3	1,467.20

Four Group Model

λ_1	0.000	λ_2	12.04	λ_3	80.57	λ_4	787.5
n_1	5,188.87	n_2	2,343.94	n_3	751.49	n_4	715.70

Nine Group Model

λ_1	0.000	λ_2	6	λ_3	24	λ_4	48	λ_5	120	λ_6	240	λ_7	360	λ_8	900	λ_9	1,800
n_1	5,188.86	n_2	1,556.66	n_3	787.28	n_4	411.53	n_5	339.96	n_6	161.03	n_7	161.03	n_8	268.38	n_9	125.24

Table 4.11: Sharing needles and syringes rates λ_i, sizes of group n_i of drug users for $i = 1, 2, ..., 9$ using data from 1990.

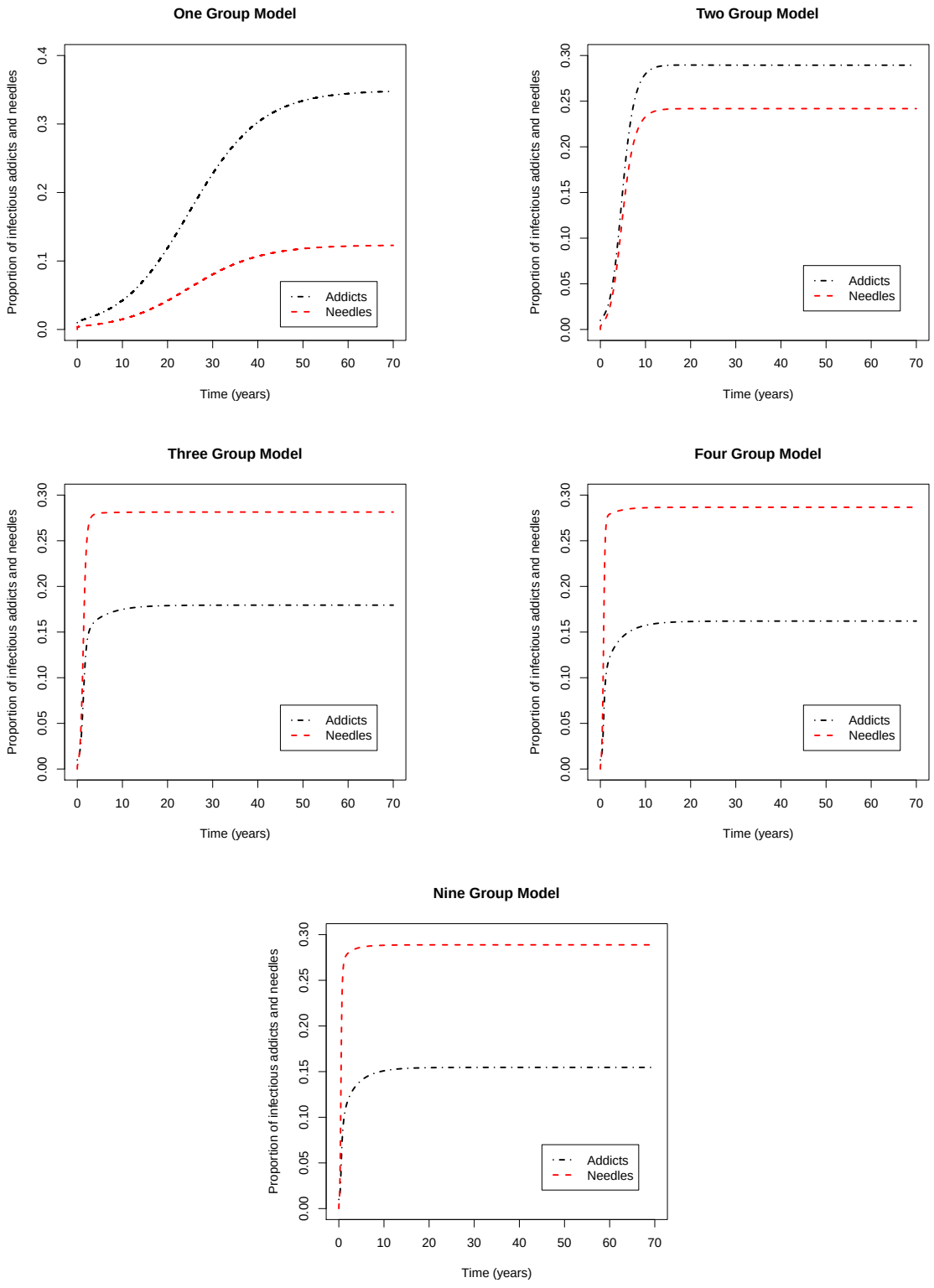


Figure 4.14: The total proportion of infectious addicts and needles in one, two, three, four and nine group models using sharing rates based on data from 1990 (Goldberg et al., 1996).

the lowest total proportions of infectious addicts which is nearly 15% and achieves a steady equilibrium solution with the following values $(\pi_x^*, \pi_{x1}^*, \pi_{h1}^*, \pi_{h2}^*, \pi_y^*, \pi_z^*) = (0.8208, 0.0123,\ 0.0117, 0.0041, 0.1386, 0.0121)$. For the needles, at each stage of infectivity, $(\beta_{h1}^*, \beta_{h2}^*, \beta_y^*)$=(0.0220,0.0077,0.2590). Figure 4.14 displays the total proportion of infectious addicts and needles in the three, four and nine group models, where we can see that the disease takes off in these models and also achieves a steady equilibrium solution in each model for both addicts and needles.

4.8 Comparing all Models

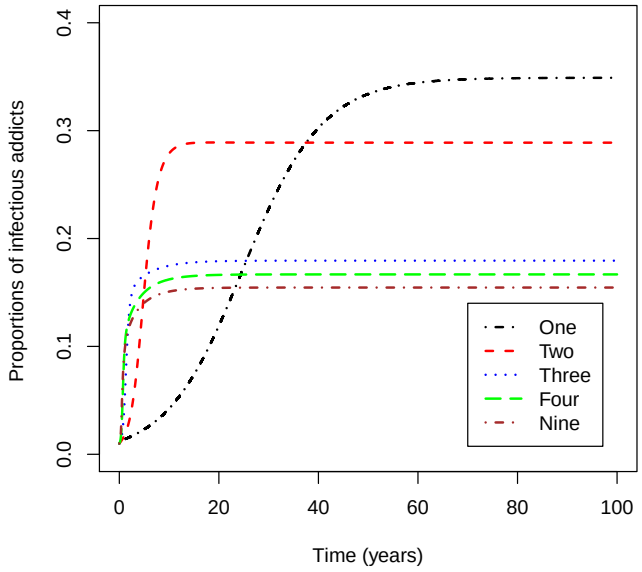


Figure 4.15: Comparing all the proportions of infectious addicts for all models using sharing rates of data from 1990 (Goldberg et al., 1996).

4.8.1 Infectious Addicts

As we did in each different set of data, we compare the infectious addicts together in one graph to understand the real impact of heterogeneity on the spread of HCV amongst drug users. Clearly we can see from Figure 4.15 that the homogeneous model has the highest endemic equilibrium prevalence of infectious addicts and the most heterogeneous model (the nine group model) has the lowest. Also, as the number of groups increased the basic reproductive number in each model increased too. Therefore, these simulation results are consistent with our theoretical results which show that in this situation the homogeneous model has the lowest value of R_0.

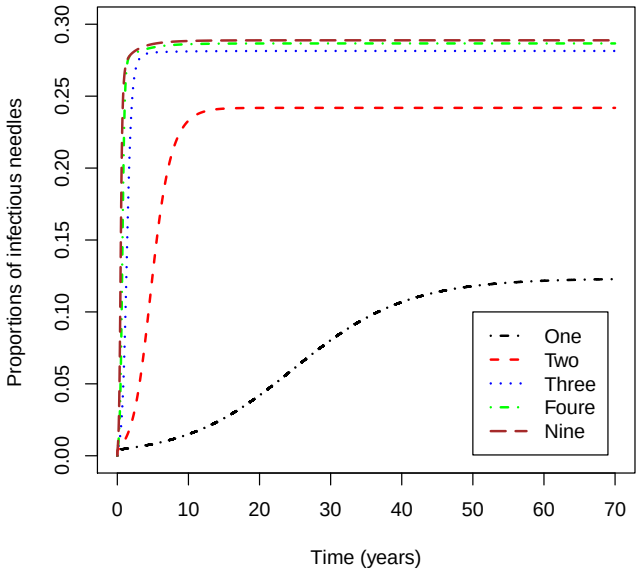


Figure 4.16: Comparing all the proportions of infectious needles for all models using sharing rates of data from 1990 (Goldberg et al., 1996).

4.8.2 Infectious Needles

As in earlier simulation results, we assume that the addicts share their needles in one shooting gallery, Figure 4.16 shows the total proportions of infectious needles in all five different models. Clearly, we can see from this figure that the more groups there are, the bigger R_0 is, and the higher the endemic equilibrium proportions of infectious needles are. The homogeneous model has the lowest endemic equilibrium proportion at about 12% and the nine group model has the highest at about 28%. We also find that the three, four, five, six, seven and nine group models (five, six and seven not presented) are similar to each other with nearly 28% of total endemic equilibrium proportions of infectious needles.

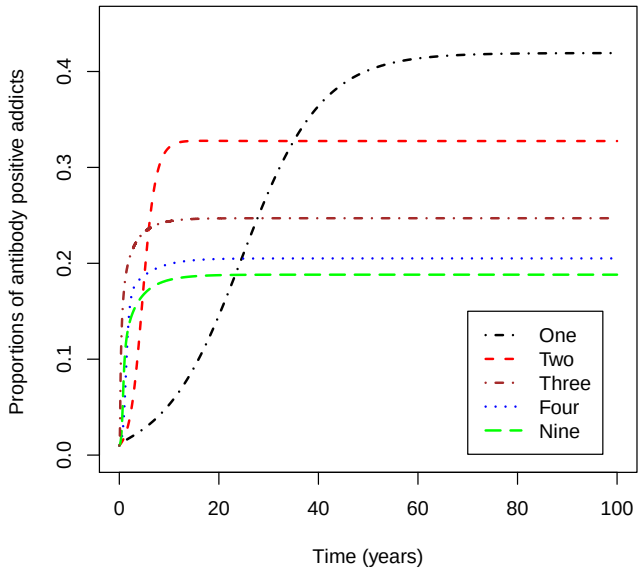


Figure 4.17: Comparing all the proportions of antibody positive addicts for all models using sharing rates of data from 1990 (Goldberg et al., 1996).

4.8.3 Antibody Positive Addicts

Now we aim to discuss briefly the antibody positive addicts in all five models. For this data from 1990 we find that the pattern is similar to the total proportion of infected addicts. Figure 4.17 shows that the disease takes off fastest in the nine group model, however this model has the lowest endemic equilibrium proportion antibody positive of nearly 17%. The homogeneous model has the highest endemic equilibrium proportions with 42%. Again, we can see from Figure 4.17 that the four and nine group models behave similarly.

4.9 Hypothetical Sharing Rates

We have simulated the mathematical models of the prevalence of HCV among drug addicts using the sharing rates which are calculated from a survey in Glasgow in 1990 and 1993 (Hutchinson et al., 2000). The simulation results demonstrate that the disease will take off in both cases as R_0 was always above unity. Now we attempt to simulate our model according to similar conditions and parameters estimations as above, however, R_0 is under unity. The approach is similar to what we have done for the data for the six months periods from 1990 and 1993, however we assume hypothetical sharing rates λ_i which ensure that in the homogeneous case $R_0 \leq 1$. We shall illustrate that it is possible for the disease to die out in the homogeneous model and tends to the disease-free equilibrium. However, in the heterogeneous models, $R_0 > 1$ and the disease tends to the unique endemic equilibrium. For this purpose we use the data of sharing borrowed used needle rates λ_i^* in the six month period which was taken in 1993 (Hutchinson et al., 2000) in place of λ_i without increasing

them to include the effect of sharing unused needles. Table 4.12 presents the sharing rates of each of the models.

4.9.1 One Group Model

First we simulate the homogeneous case using our hypothetical sharing rates. The sharing rate is estimated from data for 1993, to be $\lambda = 39.2$ per year. We estimate $R_0 = 0.55 < 1$ using the other model parameters as in Table 4.3. The results are displayed in Figure 4.18. As before we assume that initially 1% of addicts are in the acute infectious h_1 class, the remaining 99% are in the susceptible x class and no needles are infected. From Figure 4.18 we can see that the disease dies out. This agrees with our earlier analytical results and the results of Corson et al. (2012) which predict that if $R_0 \leq 1$ then the disease will die out in addicts and needles. In this model, the overall proportions of infected addicts and needles tend to disease-free equilibrium, these are presented in Tables 4.14 and Table 4.15. Thus, the simulation results are compatible with the theoretical results where if $R_0 \leq 1$ the model has a disease-free equilibrium.

4.9.2 Two Groups Model

Next we discuss the impact of heterogeneity of our model by generating two groups of addicts according to their sharing rates and using the hypothetical sharing rates using data of drug users in Glasgow for 1993. The first group never share needles, $\lambda_1 = 0$ per year and the second group share needles and syringes at rate $\lambda_2 = 120.2$ per year. As earlier we assume that initially 99% of addicts in each group are in the x-susceptible class and the remaining 1% are h_1-infected addicts. There are no

One Group Model

λ	39.2
n	9,000

Two Group Model

λ_1	0.000	λ_2	120.18
n_1	6,065.61	n_2	2,934.39

Three Group Model

λ_1	0.000	λ_2	62.6	λ_3	605.65
n_1	6,065.61	n_2	2,648.11	n_3	286.28

Four Group Model

λ_1	0.000	λ_2	62.6	λ_3	306.16	λ_4	990.7
n_1	6,065.61	n_2	2,648.11	n_3	161.03	n_4	125.24

Six Group Model

λ_1	0.000	λ_2	10.95	λ_3	87.33	λ_4	237.25	λ_5	306.16	λ_6	990.7
n_1	6,065.61	n_2	1,735.58	n_3	465.20	n_4	447.31	n_5	161.03	n_6	125.24

Nine Group Model

λ_1	0.000	λ_2	10.95	λ_3	51.1	λ_4	129.6	λ_5	237.25	λ_6	259.1	λ_7	365	λ_8	912.5	λ_9	1,460
n_1	6,065.61	n_2	1,735.58	n_3	250.49	n_4	214.71	n_5	447.31	n_6	89.46	n_7	71.57	n_8	107.35	n_9	17.89

Table 4.12: Hypothetical sharing needles rates λ_i, sizes of group n_i of drug users for $i = 1, 2, ..., 9$ using data from 1993.

other infected addicts or needles. Using the parameter estimates in Table 4.3 we estimate that $R_0 = 1.7 > 1$, so unlike the one group model the disease does not die out. We can see from Figure 4.18 that the disease persists in both addicts and needles. Moreover, the overall steady state values of infectious addicts and needles are presented in Table 4.14 and Table 4.15.

Model	R_0	Infectious addicts	Infectious needles	Antibody positive
One group	0.55	0%	0%	0%
Two group	1.71	12%	8%	15%
Three group	4.7	11%	12%	14%
Four group	6.05	11%	12%	13%
Six group	6.82	9%	14%	11%
Nine group	7.06	9%	14%	11%

Table 4.13: Comparing the six models in the basic reproductive numbers and equilibrium percentage of proportions of infectious addicts, needles and antibody positive addicts using hypothetical sharing rates of data from 1993.

4.9.3 Three and Four Groups Models

Now we divide the population into three and four groups and examine the behaviour of the disease among drug addicts. In the three groups model and using the parameters in Table 4.3 and for $p = 3$, $\lambda_1 = 0$, $\lambda_2 = 62.6$, and $\lambda_3 = 605.65$ per year, we deduce that $R_0 = 4.7 > 1$. As earlier we assume that at time $t = 0$, for $i = 1, 2, 3, 4$, $\pi_{xi}(0) = 0.99$, $\pi_{x_1 i}(0) = 0$, $\pi_{h_1 i}(0) = 0.01$, $\pi_{h_2 i}(0) = \pi_{yi}(0) = \pi_{zi}(0) = 0$. Similarly, for infectious needle fractions at time $t = 0$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = 0$. We can see from Figure 4.18 that the three group model is similar to the four group model in both infectious addicts and needles. These models also achieve a steady state where

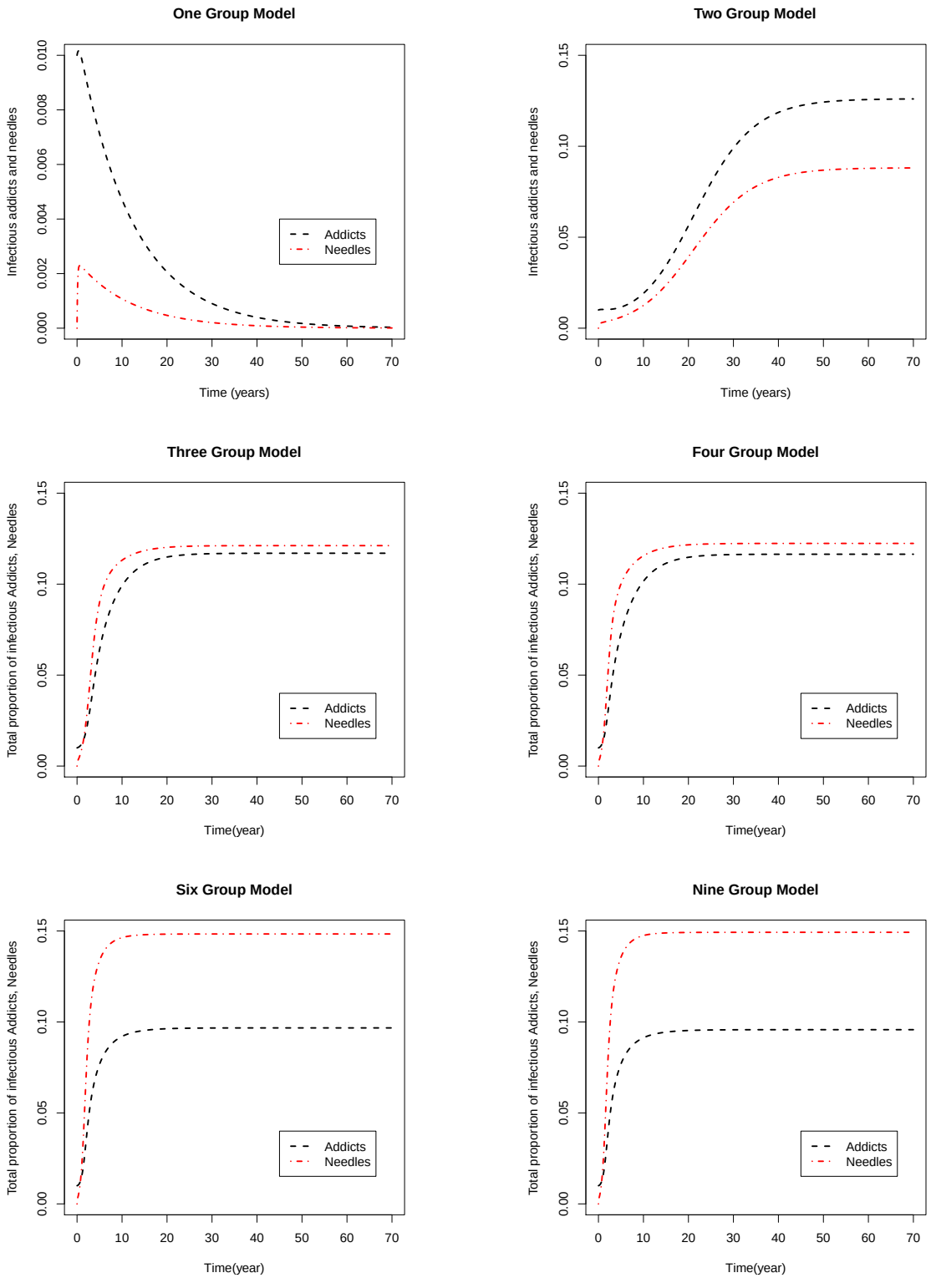


Figure 4.18: The total proportion of infectious addicts and needles in Glasgow using hypothetical sharing rates based on data from 1993.

the values are displayed in Tables 4.14 and Table 4.15. The basic reproductive numbers of these models are shown in Table 4.13.

4.9.4 Six and Nine Groups Models

More simulation models are designed to predict the disease spread in a six groups model and nine groups model using data from survey of drug addicts in Glasgow in 1993 (Hutchinson et al., 2000). In the six group model, six different sharing rates are used as follows: $\lambda_1 = 0,\ \lambda_2 = 10.95,\ \lambda_3 = 87.33,\ \lambda_4 = 237.25,\ \lambda_5 = 306.16$ and $\lambda_6 = 990.7$ per year. The set of parameter estimates in Table 4.3 are used to calculate $R_0 = 6.82 > 1$.

On the other hand, in the nine groups model, nine different sharing rates are used as follows $\lambda_1 = 0,\ \lambda_2 = 10.95,\ \lambda_3 = 51.1,\ \lambda_4 = 129.6,\ \lambda_5 = 237.25,\ \lambda_6 = 259.1,\ \lambda_7 = 365,\ \lambda_8 = 912.5$ and $\lambda_9 = 1,460$ per year. With these sharing rates and the set of parameter estimates in Table 4.3 we calculate $R_0 = 7.066 > 1$. In both models, the disease reaches a steady equilibrium solution after ten years. The equilibrium solution for the six groups model is displayed in Tables 4.14 and 4.15. From Figure 4.18 we can see the proportions of infectious addicts and needles at each stage of infectivity achieve a steady equilibrium stage after ten years in both six and nine group models. These two models appear to behave similarly to each other. Table 4.15 displays the endemic equilibrium solutions of the six different models in the h_1 and h_2 acute and the chronic y stages. From this table we can see that as the number of groups of models increases, the endemic equilibrium solutions increase too.

Models	π_x^*	$\pi_{x_1}^*$	$\pi_{h_1}^*$	$\pi_{h_2}^*$	π_y^*	π_z^*
One group	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Two group	0.8481	0.0159	0.0096	0.0033	0.1130	0.0099
Three group	0.8597	0.0142	0.0089	0.0031	0.1047	0.0092
Four group	0.8601	0.01441	0.0088	0.0031	0.1043	0.0091
Six group	0.8865	0.0090	0.0073	0.0025	0.0861	0.0076
Nine group	0.8876	0.0089	0.0073	0.0025	0.0859	0.0075

Table 4.14: Comparing the endemic equilibrium proportions of infectious addicts for all models using hypothetical sharing rates of data from 1993.

Models	$\beta_{h_1}^*$	$\beta_{h_2}^*$	β_y^*
One group	0.0000	0.0000	0.0000
Two group	0.0067	0.0023	0.0790
Three group	0.0092	0.0032	0.1084
Four group	0.0093	0.0032	0.1095
Six group	0.0113	0.0039	0.1331
Nine group	0.0114	0.0040	0.1341

Table 4.15: Comparing the endemic equilibrium proportions of infectious needles for all models using hypothetical sharing rates of data from 1993.

4.10 Comparison of Models with Different Numbers of Groups

4.10.1 Infectious Addicts

Simulations of data of the survey of Glasgow drug users in 1993 are displayed for all six models together (one, two, three, four, six and nine group models). We shall apply these data to present the cases where the disease dies out in the homogeneous case, and takes off in the heterogeneous cases.

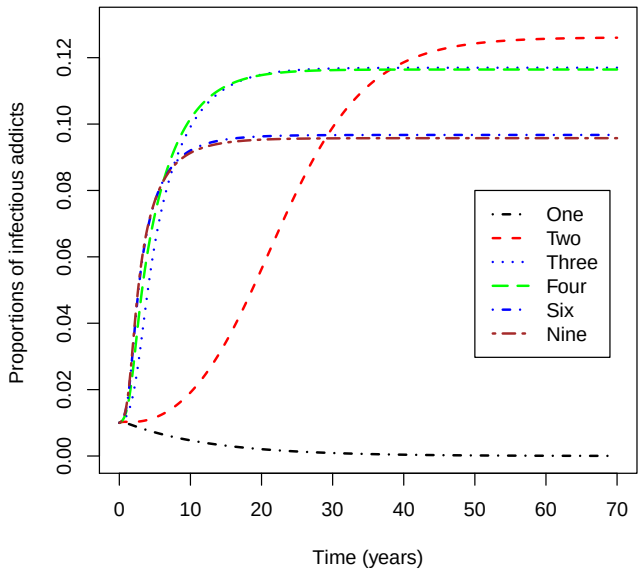


Figure 4.19: Comparing all the proportions of infectious addicts for all models using hypothetical sharing rates of data from 1993.

It is observed from Figure 4.19 and Table 4.13 that the highest overall proportion of prevalence of HCV is in the two group model which is nearly 12%, whilst the lowest proportion is in the homogeneous case which is nearly zero. Again we can

see that as the number of groups increases the initial speed of increase of the epidemic (which is related to R_0) increases. So our simulations are consistent with our theoretical results which show that in this situation the homogeneous model has the lowest value of R_0 where the disease dies out. It can be seen from Table 4.13 that the basic reproductive numbers are increased with the increasing of number of groups in each model. We can see that the nine group model has the highest value of R_0, whilst the two group model has the highest rate of prevalence of HCV among addicts.

Beyond the similarity of the HCV prevalence between the three and four group model. Figure 4.19 shows that heterogeneity is effective in increasing the initial speed of the increase of disease among drug users. Also, we notice that the six and nine group models are similar. On the other hand, increasing the number of groups increases the basic reproductive number. Conversely, increasing the number of groups (from the two group to the nine group models) reduces the equilibrium prevalence of HCV among drug users as can be seen clearly in Figure 4.19. Table 4.13 indicates the total proportions of infectious addicts, infectious needles and HCV antibody positive addicts after seventy years. The endemic equilibrium prevalence for all models in each stage, x and x_1 susceptible, h_1 and h_2 acute, chronic y and immune z are presented in Table 4.14.

4.10.2 Infectious Needles

Again we consider one shooting gallery where all the groups of drug users share the needles and syringes, however there is a significant difference between the prevalence of HCV in the needles. Figure 4.20 illustrates that both the six and nine group

models have the highest equilibrium proportions of infectious needles which is nearly 14%.

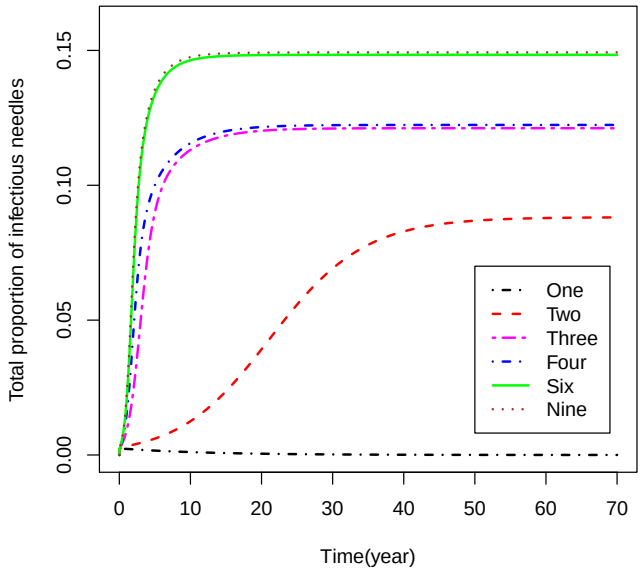


Figure 4.20: Comparing all the proportions of infectious needles for all models using hypothetical sharing rates of data from 1993.

On the other hand, the one group model has the lowest equilibrium proportion of infectious needles. We can see from Figure 4.20 that the three and four group models behave similarly, and the six and nine groups models are similar. In these simulation results, we can see that increasing the number of groups increases the total proportions of infectious needles. Also, in the one group model where $R_0 < 1$, it appears that the disease dies out in the needles and as $R_0 > 1$ in the rest of the five models the disease takes off in the needles in the shooting gallery.

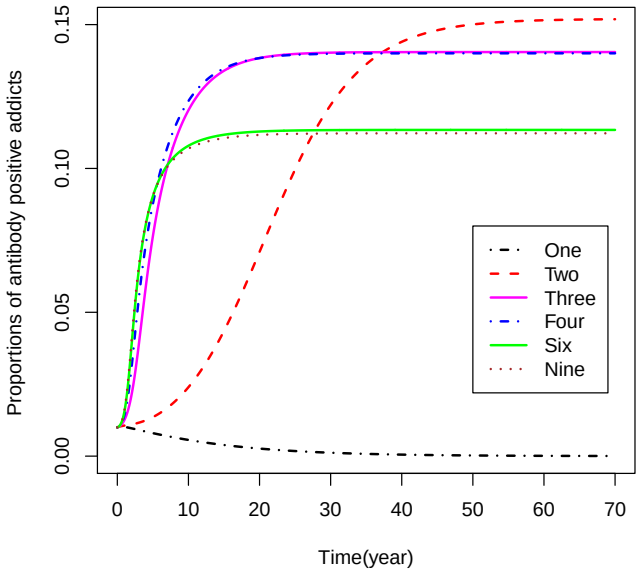


Figure 4.21: Comparing all the proportions of antibody positive addicts for all models using hypothetical sharing rates of data from 1993.

4.10.3 Antibody Positive Addicts

Now, we shows the simulation results of the long term proportions of the antibody positive addicts. Table 4.13 represents these proportions using the hypothetical sharing rates of data from 1993 (Hutchinson et al., 2000). As in earlier simulations, the antibody positive classes are the susceptible x_{1i}, acutely infected h_{1i} and h_{2i}, chronically infected y_i and immune z_i, for $i = 1, 2, ..., p$. The results are displayed in Figure 4.21, where we can see that the homogeneous model has the lowest equilibrium proportion of antibody positive addicts. Again, the pattern is similar to the total proportion of infected addicts using the hypothetical sharing rates of data from 1993.

4.11 Conclusion

In this chapter, we have performed numerical simulation on the system (2.1) - (2.9) describing the spread of hepatitis C amongst injecting drug users. We started off with a literature review to identify values for the relevant parameters. Then we presented some simulation results using data from a survey of injecting drug users in 1990. The reported rates at which addicts said that they used a needle previously used by someone else had to be converted into the rates at which addicts shared both used and unused needles. The simulations were repeated dividing the addicts into different groups according to the sharing rate with the number of groups varying from one to nine. In each case the overall average needle sharing rate was kept the same. We calculated the basic reproductive number for each scenario and presented simulations comparing the total proportion of infected addicts, the total proportion of infected needles and the total proportion of antibody positive addicts. The disease took off in each model. Then we repeated this analysis using data from a second survey of injecting drug users taken in 1993.

To widen our simulation scenario we then used results from a second survey of drug users in 1990 (Goldberg et al., 1996) to compare the results with those of Greenhalgh (1997) for HIV/AIDS amongst drug users and to obtain a broader spectrum of theoretical simulation results we did not correct the sharing rates. Although it would have been more realistic to do this if we had done it the results would have been very similar to our previous results. Then we repeated the exercise for the simulation using the data of 1993 for HCV without this correction. This produces a

(theoretical) situation where R_0 is less than one for the homogeneous model but as the number of groups increases R_0 exceeds one.

In this chapter we have assumed that there is one shooting gallery where all addicts share needles. We divide the addict population into different numbers of groups with different sharing rates. As the number of groups increased R_0 also increased. The initial rate of increase of the level of disease also increased with the number of groups as did the endemic equilibrium prevalence of HCV amongst needles. However, both the endemic equilibrium proportion of HCV amongst addicts and the endemic equilibrium number of HCV antibody positive addicts shows the opposite pattern. There as the number of groups increased the endemic prevalence of HCV amongst addicts and the endemic equilibrium number of HCV antibody positive addicts decreased as the number of groups increased. These results are qualitatively similar to those obtained by Greenhalgh (1997) for the spread of HIV/AIDS amongst injecting drug users.

In the next chapter we shall look at the effects of heterogeneity of probability of visiting shooting galleries. For simplicity we assume that there is one group of addicts and two shooting galleries. We perform a numerical simulation for three models. Each model has two different visiting probabilities P_1 and P_2 and is simulated for both cases where R_0 exceeds and is beneath unity. Then we look at a more complicated case, as we assume that there are two groups of addicts who visit two shooting galleries. We show the numerical simulation results, and confirm that R_0 is a sharp threshold which determines whether the disease takes off or dies out.

Chapter 5

Simulations on Heterogeneity of Visiting Shooting Galleries

In this chapter we continue to present more numerical simulation results. We shall focus on the effects of heterogeneity of visiting shooting galleries. In Chapter Four we have assumed that this parameter is homogeneous where addicts share needles in one shooting gallery. Now we shall discuss the impact of heterogeneity of visiting shooting galleries on the behaviour of HCV among addicts and needles. Before we start our analysis of the simulation where there is more than one shooting gallery, we should remind ourselves of the definition of a shooting gallery. This is a place where addicts meet to inject and share drugs. Kimber & Dolan (2007) say that one example of a shooting gallery is an illegal off-street space near to drug markets used for drug injection.

The first section discusses the simulation results of the heterogeneity effect of one group of addicts visiting two shooting galleries at different probabilities. Then

we move to the more complicated case where there are two groups of addicts visiting two shooting galleries with different probabilities.

Parameter	Definition	Estimate
ϕ_{ij}	Probability that an addict in group i cleans a needle in shooting gallery j before use, $i = 1,\ j = 1, 2$.	0.255
λ_i	Needle and syringe sharing rate in group i, $i = 1$.	167.39 per year
τ_j	Needle turnover rate in shooting gallery j, $j = 1, 2$.	133 per year
μ	Per capita rate at which addicts leave the sharing, injecting population.	0.17 per year
α_h	Acute HCV transmission probability per injection.	0.0432
α_y	Chronic HCV transmission probability per injection.	0.016
$1/\sigma$	Average duration of the acute stage.	0.5 years
δ	Proportion of acutely infected addicts who resolve HCV infection.	0.26
α	The proportion of those addicts spontaneously resolving HCV infection who become immune.	0.25
m_j	Number of needles in shooting gallery j, $j = 1, 2$.	4,491

Table 5.1: Table of parameter estimates used in our simulations.

5.1 One Group of Addicts and Two Shooting Galleries

Due to the lack of data in this area and for simplicity, we are assuming that we have two shooting galleries and one group of addicts. Thus, addicts visit shooting gallery one with the probability P_1, similarly addicts choose shooting gallery two

with probability P_2. Then, we will study the effects of heterogeneity in both sharing rate and probability of visiting of shooting gallery. We will examine the simulation results where $R_0 > 1$ and where $R_0 \leq 1$ to compare the results of our model in each different case.

5.1.1 Simulation Results

In the last chapter we calculated the sharing rates λ which are found by the survey taken of addicts from Glasgow by HPS in 1990 (Hutchinson et al. (2000)). As we are assuming that the addicts are homogeneous in sharing needles rate, we found that $\lambda = 167.39$ per year. The total number of current addicts in Glasgow is approximately 9,000 (NESI, 2010). Thus, using $\gamma = 1.002$ we find that the total number of needles in all shooting galleries is $m = 8,982$. We are assuming that we have two shooting galleries, and shooting gallery one has $m_1 = m/2 = 4,491$ needles and shooting gallery two has $m_2 = m/2 = 4,491$ needles. Table 5.1 presents the estimated parameters of our model which we used in the last chapter.

In each model simulation, we assume that at time $t = 0$, $\pi_x(0) = 0.99$, $\pi_{x_1}(0) = \pi_{h_2}(0) = \pi_y(0) = \pi_z(0) = 0$ and $\pi_{h_1}(0) = 0.01$. So 99% of addicts were not infected while 1% of addicts were in the acute h_1 stage. Similarly for the fractions of infectious needles at time $t = 0$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = \beta_{h_1 2}(0) = \beta_{h_2 2}(0) = \beta_{y2}(0) = 0$. Thus, all the needles in shooting gallery one and shooting gallery two are disease-free.

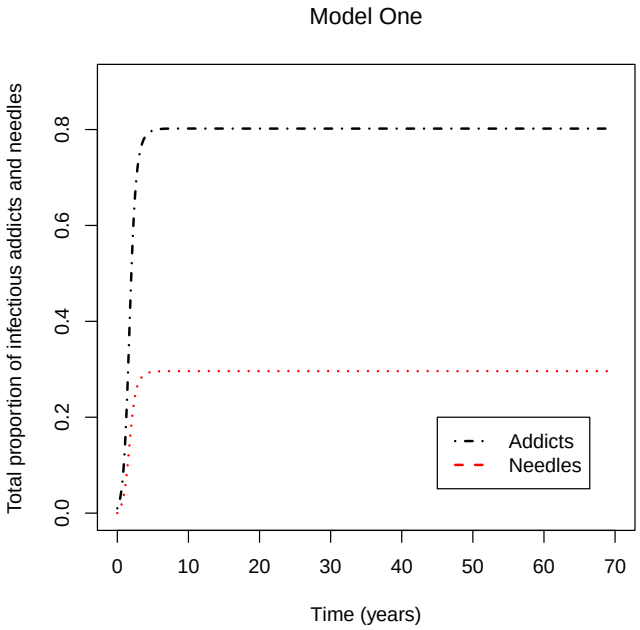


Figure 5.1: The total proportions of infectious addicts and needles where $P_1 = 0.01$ and $P_2 = 0.99$.

5.1.2 Model One

A simulation is performed for HCV prevalence for $q = 2$ shooting galleries. In model one, we have assumed that the probability of visiting shooting gallery one is $P_1 = 0.01$ and the probability of visiting shooting gallery two is $P_2 = 0.99$. Using the estimation of parameters in Table 4.3 we estimate $R_0 = 7.1872$, using the formulae (2.19) and (2.20). As we have two shooting galleries visited by one group of addicts, thus from equation (2.23):

$$R_0 = \xi \left(\frac{n\lambda^2 \frac{P_1^2}{m_1}(1-\phi)}{n\frac{\lambda P_1}{m_1} + \tau} + \frac{n\lambda^2 \frac{P_2^2}{m_2}(1-\phi)}{n\frac{\lambda P_2}{m_2} + \tau} \right). \tag{5.1}$$

In this model the fraction of infected addicts $(\pi_{h_1} + \pi_{h_2} + \pi_y)$ is approximately 80%, which implies that the total proportion of infectious addicts at equilibrium is

high. Figure 5.1 shows that the total endemic equilibrium proportion of infectious needles in model one is nearly 29%. The model has reached an equilibrium state after about 3 - 4 years and the estimated steady state values are $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.1133, 0.0214, 0.0611, 0.0214, 0.7193, 0.0631)$. For needles at each stage of infectivity $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0.0225, 0.0079, 0.2656)$.

5.1.3 Model Two

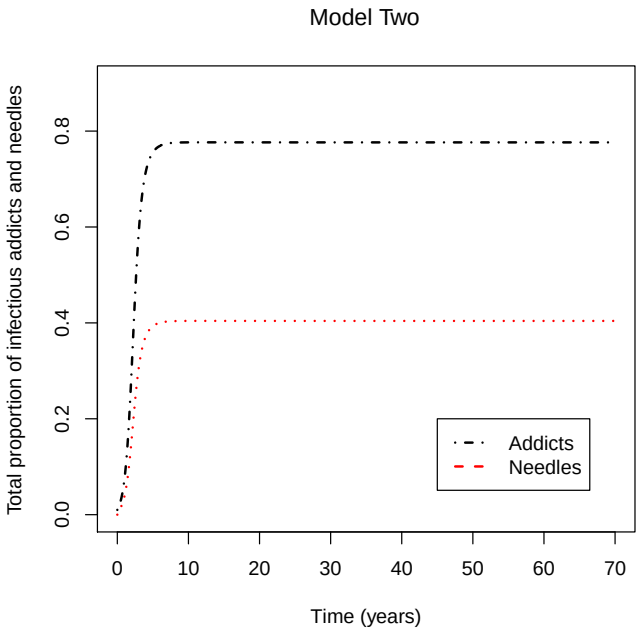


Figure 5.2: The total proportions of infectious addicts and needles where $P_1 = 0.25$ and $P_2 = 0.75$.

Then, we performed a simulation in model two where we are assuming that $P_1 = 0.25$ and $P_2 = 0.75$ for shooting gallery one and two respectively. R_0 is estimated to be 5.9038 using formula (5.1). Also, similar values of other parameters are used to simulate our model. Figure 5.2 displayed the simulation results of total infectious addicts and needles in this case. Clearly, we can see that total equilibrium infectious

proportion of addicts is nearly 77%. Moreover, the total equilibrium proportion of infectious needles in all shooting galleries is about 40%. The steady state values of this model are $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.1371, 0.0251, 0.0592, 0.0208, 0.6964,\ 0.0611)$. For needles at each stage of infectivity $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0.0308, 0.0108, 0.3624)$.

5.1.4 Model Three

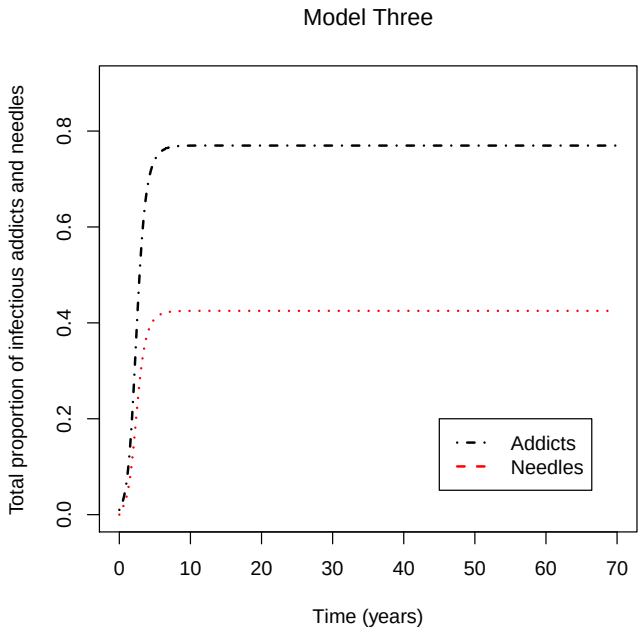


Figure 5.3: The total proportions of infectious addicts and needles where $P_1 = 0.40$ and $P_2 = 0.60$.

Finally, we simulate our model assuming that addicts visit shooting gallery one with probability $P_1 = 0.4$, and visit shooting gallery two with probability $P_2 = 0.6$. In this case, we estimate $R_0 = 5.62$ using formula (5.1) and as can be seen from Figure 5.3 the total equilibrium proportion of infectious addicts is about 76% while the total equilibrium proportion of infectious needles is approximately 42%. Again, we can see that the model has an equilibrium state where the addict steady state values

are $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.1435, 0.0261, 0.0586, 0.0206, 0.6904, 0.0606)$, for the needles the steady state values are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0.0324, 0.0113, 0.3812)$.

5.2 Comparison of the Three Models

5.2.1 Infectious Addicts

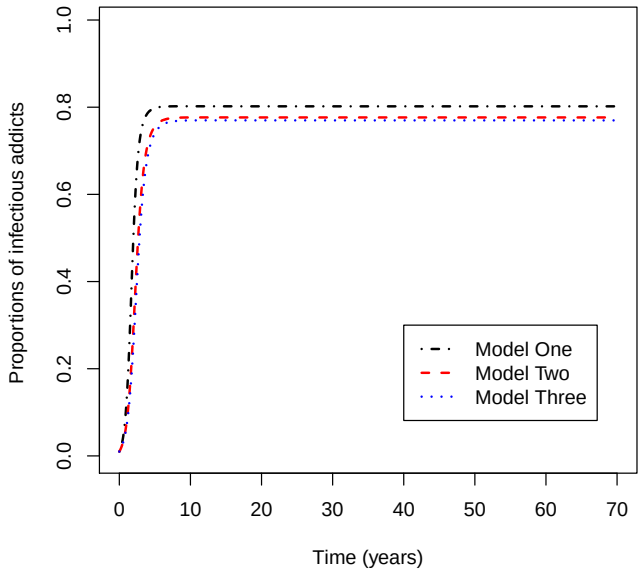


Figure 5.4: The total proportions of infectious addicts in the three models.

This section describes the different behaviour of the three models with three different probabilities of the addicts visiting shooting galleries. Figure 5.4 shows the plots of these proportions. The main goal of this work is to analyze the effects of heterogeneity of visiting shooting galleries. In model one where the difference between the visiting probabilities for the two shooting galleries is the biggest, we found that the value of R_0 is the biggest. However, as we examine different probabilities of visiting shooting

galleries (1% and 99%, 25% and 75%, 40% and 60%), there is no significant difference between the three models. In all models, we find $R_0 > 1$. Thus we can see that the disease takes off in all models, and tends to an equilibrium steady state with time.

5.2.2 Infectious Needles

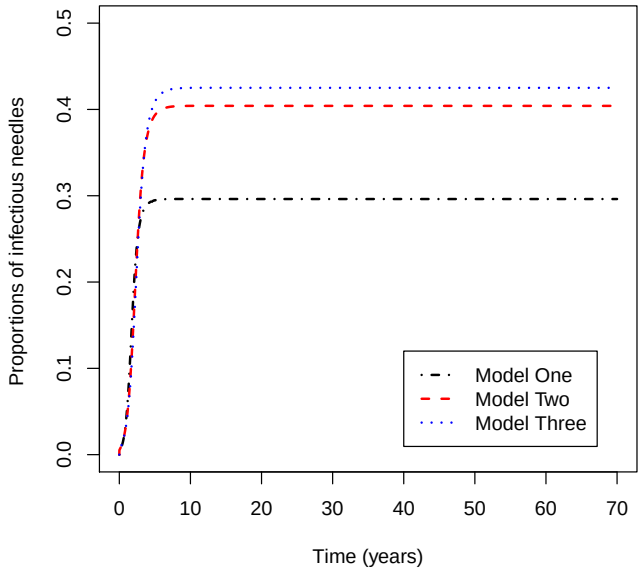


Figure 5.5: The total proportions of infectious needles in the three models.

To analyze the effects of heterogeneity of visiting shooting galleries, three models were compared in Figure 5.5. For simplicity, we assume that we have two shooting galleries where the addicts share needles and syringes. Then, we assume that there are three different sets of probabilities of visiting these galleries (1% and 99%, 25% and 75%, 40% and 60%). Figure 5.5 shows the total proportions of infectious needles in shooting gallery one and two together. Clearly, we can see as the difference between P_1 and P_2 decreases the value of R_0 decreases and the equilibrium proportions of

infectious needles increase. Again, as $R_0 > 1$, we expect the disease to be present in all shooting galleries. For these simulations the model with the more heterogeneity in visiting shooting galleries (model one), has the lowest equilibrium proportion of infectious needles (29%).

5.2.3 Antibody Positive Addicts

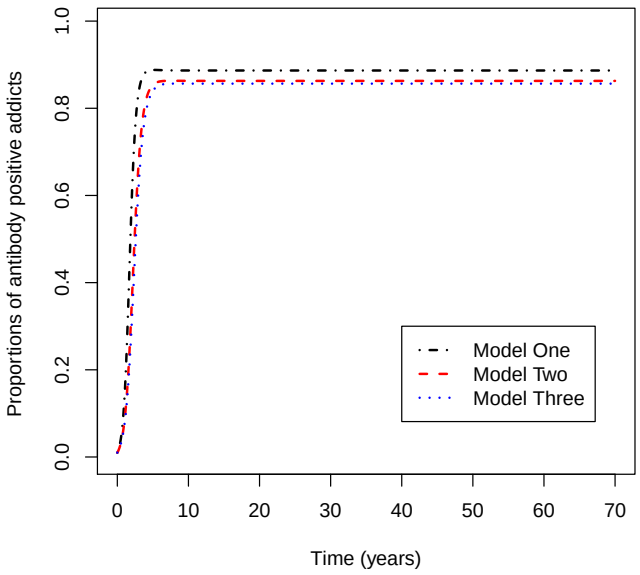


Figure 5.6: The total proportions of antibody positive addicts in the three models.

Although the prevalence of HCV amongst addicts population is a statistic of interest, Health Protection Scotland collects data on the proportion of antibody positive addicts. Hence it is important to look at the level of antibody positive addicts in the three models. We remind the reader that the HCV antibody classes are the susceptible π_{x_1}, acutely infected π_{h_1} and π_{h_2}, chronically infected π_y and immune π_z classes. The results of the simulations of the proportions of antibody positive addicts in the

three models are displayed in Figure 5.6. We can see that although the three models have three very different sets of shooting galleries visiting probabilities, these models behave similarly. The highest equilibrium proportion of antibody positive addicts is in model one (88%) and the lowest is in model three (85%).

5.3 Two Groups of Addicts Visiting Two Shooting Galleries

Our aim in this section is to demonstrate numerically the analytical results found previously, that is if $R_0 < 1$ then the disease dies out and if $R_0 \geq 1$ then the disease takes off. In the previous section we demonstrated that this was the case for one group of addicts visiting two shooting galleries. Each group shares needles at a different rate so we choose $\lambda_1 = 65$ per year and $\lambda_2 = 10$ per year. We alter the probabilities P_{ij} to give $R_0 \leq 1$ for the first set of parameters and $R_0 > 1$ for the second set of parameters. We keep the estimates for the other parameters as in the above simulation.

5.3.1 Simulation when $R_0 \leq 1$

As stated above we assume that the sharing rate for the first group of addicts is $\lambda_1 = 65$ per year and for the second group of addicts $\lambda_2 = 10$ per year. We assume that group one of addicts visit shooting gallery one with probability $P_{11} = 0.45$ and shooting gallery two with probability $P_{12} = 0.55$ and that addicts in group two visit shooting gallery one with probability $P_{21} = 0.85$ and shooting gallery two with

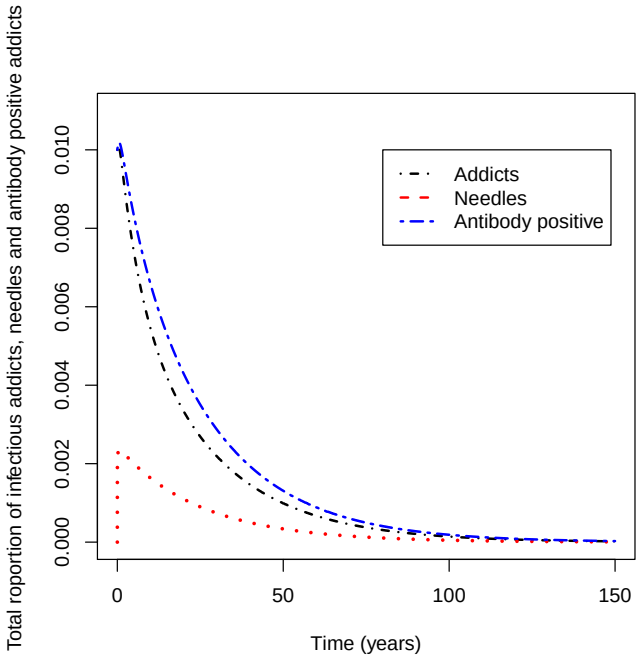


Figure 5.7: The total proportions of infectious addicts, needles and antibody positive addicts for parameter values where $R_0 = 0.8$.

probability $P_{22} = 0.15$. In this case recall that R_0 is the spectral radius of the matrix:

$$\mathbf{Q} = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix},$$

where for $i, k = 1, 2$

$$\begin{aligned} Q_{ik} &= \xi(1-\phi)\sum_{j=1}^{2} \frac{\lambda_i P_{ij} \Lambda_{kj}}{\Lambda_{1j} + \Lambda_{2j} + \tau}, \\ &= \xi(1-\phi)\lambda_i \lambda_k n_k \left(\frac{P_{i1}P_{k1}}{m_1(l_1+\tau)} + \frac{P_{i2}P_{k2}}{m_2(l_2+\tau)} \right), \end{aligned}$$

where $l_1 = \frac{n_1\lambda_1 P_{11}}{m_1} + \frac{n_2\lambda_2 P_{21}}{m_1}$ and $l_2 = \frac{n_1\lambda_1 P_{12}}{m_2} + \frac{n_2\lambda_2 P_{22}}{m_2}$. The characteristic equation of this matrix is:

$$(Q_{11} - \omega)(Q_{22} - \omega) - Q_{12}Q_{21} = 0,$$

and its spectral radius is

$$R_0 = \frac{1}{2}\Big(Q_{11} + Q_{22} + \sqrt{(Q_{11} - Q_{22})^2 + 4Q_{12}Q_{21}}\ \Big). \tag{5.2}$$

Then we find that $R_0 = 0.8 < 1$ which implies that whatever the starting values the disease dies out in all addicts groups and needles in shooting galleries.

The simulations were repeated with a variety of starting values and parameters which gave $R_0 < 1$ and in each case the disease ultimately dies out in addicts and needles. A typical simulation is shown in Figure 5.7. As earlier we assume that at time $t = 0$, $\pi_{xi}(0) = 0.99$, $\pi_{x_1 i}(0) = 0$, $\pi_{h_1 i}(0) = 0.01$, $\pi_{h_2 i}(0) = \pi_{yi}(0) = \pi_{zi}(0) = 0$ for $i = 1, 2$. Similarly, for infectious needle fractions at time $t = 0$, $\beta_{h_1 j}(0) = \beta_{h_2 j}(0) = \beta_{yj}(0) = 0$ for $j = 1, 2$. The simulation is performed over a hundred and fifty year time period so that we can clearly see that the disease dies out and the system tends to the disease-free equilibrium where $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (1, 0, 0, 0, 0, 0)$, and the needles steady-state values are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0, 0, 0)$. In the next section we will look at the simulation results when R_0 exceeds unity.

5.3.2 Simulation when $R_0 > 1$

To examine the behaviour of HCV in the case where there are two groups of addicts and two shooting galleries when $R_0 > 1$, we keep the same needle sharing rates for the two groups; also we keep the probabilities of group two visiting the two shooting galleries. However, we assume that the addicts in group one visit the shooting galleries with probabilities $P_{11} = 0.99$ and $P_{12} = 0.01$ respectively. All of the other parameters and the initial starting values are the same as in the simulation above.

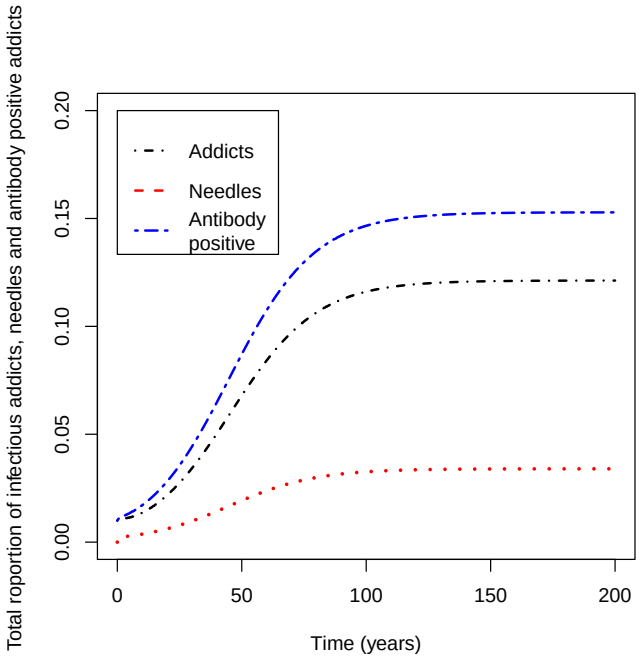


Figure 5.8: The total proportions of infectious addicts, needles and antibody positive addicts for parameter values where $R_0 = 1.28$.

From Figure 5.8 we can see that the disease persists in addicts, needles in shooting galleries and antibody positive addicts. We can see clearly that the model has an equilibrium state where the addicts steady state values are $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.8533, 0.0214, 0.0089, 0.0031, 0.1039, 0.0091)$, and the needles steady state values are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0.0025, 0.0009, 0.0291)$.

5.4 Conclusion

In this chapter we have considered the heterogeneity of visiting shooting galleries. Numerical simulations were used to describe the spread of HCV among addicts in different groups and needles in different shooting galleries. In the light of the lack of data of the shooting galleries' visiting probabilities, we estimated these parameters. First, the simplest case discussed is where we assumed that we have a homogeneous

society of addicts and two shooting galleries. An explicit expression of R_0 is given, and it exceeds unity in the three models. These models are set up with three different sets of visiting probabilities.

The probabilities in model one, two and three are respectively $P_1 = 0.01,\ P_2 = 0.99,\ P_1 = 0.25,\ P_2 = 0.75$ and $P_1 = 0.4,\ P_2 = 0.6$. In each model we presented a figure of total proportions of infectious addicts and needles. Then a general comparison of these models is given of the total proportions of infectious addicts, needles and the antibody positive addicts in the three models. These figures showed that although the three models have three very different sets of shooting galleries visiting probabilities, these models behave similarly. Also a comparison of infectious needles is displayed and discussed. Nevertheless here we noticed that the heterogeneity of visiting probabilities may decrease the equilibrium level of infectious needles. The most heterogeneity is in model one where we can seen that model one has the lowest level of infectious needles.

For more understanding of the heterogeneity of P_{ij}, we simulated the total proportions of two groups of addicts visiting two shooting galleries. In this case, the sharing rates of the first group are estimated as $\lambda_1 = 65$ per year and for the second group $\lambda_2 = 10$ per year. Then, we kept these parameters and changed the probabilities of visiting of shooting galleries, P_{ij}. It was shown that the first set of assumptions gave $R_0 < 1$ and in each case the disease ultimately dies out in addicts and needles. This result showed that the disease dies out and the system tends to the disease-free equilibrium and the addicts and needles steady-state values are obtained. On the

other hand, the second set of assumptions gave that $R_0 > 1$. We have displayed that the disease persists in addicts, needles in shooting galleries and antibody positive addicts. Also, our simulation showed that the model has an equilibrium state and we obtained the addicts and needles steady state values. In the next chapter we will be concerned with the numerical demonstration of the analytical results obtained earlier in Chapter Two.

Chapter 6

Numerical Results on Optimal Epidemic Control

Earlier in Chapter Two we have shown that the basic reproductive number R_0 can be controlled (and thus the progress of the disease can be controlled) under some special scenarios. Thus we attempt to discuss some of these theoretical results numerically and present numerical simulations in each case. Recall that the basic reproductive number can be defined as the expected number of secondary cases caused by a single newly infectious case entering a disease-free population at equilibrium. One of the main results that we proved earlier states that if R_0 is less than or equal to unity then HCV will die out in both addicts groups and shooting galleries. For this reason, it is important to control the disease by making R_0 as small as it can be.

6.1 Special Scenarios

We have discussed in Chapter Two some special cases that minimise R_0 under a set of particular assumptions. Here, we shall discuss numerical illustrations of these special

cases followed by some plots to illustrate the relationship between the parameters and R_0. The first was the effect of variability in shooting gallery visiting rates on R_0 where we showed that, under the assumption that $P_{ij} = P_j$, independent of i, all addicts visiting shooting galleries at the same rate, minimises R_0. Then we shall consider the assumption where all addicts visit shooting galleries at the same rate $\overline{\lambda}$. We will start by looking at the case where we assume that all addicts are sharing needles in shooting galleries at random. First of all we discuss the effect of heterogeneity in shooting gallery visiting rates to minimise R_0, after which we will present the numerical result of how to optimally allocate needle exchange effort if the total amount of needle exchange effort available is τ. Finally, we finish with a discussion of the effect of the allocation of needle cleaning probability ϕ_{ij} to minimise R_0 if the total amount of needle cleaning kits available is fixed. We follow the theoretical results with a figure showing how R_0 varies with the needle cleaning probability ϕ_{ij}.

6.2 Numerical Results of Addicts Visiting Shooting Galleries at Different Rates

Let us consider the model where addicts choose needles at random. Recall that there are m_j needles in shooting gallery j and m needles together, so $P_{ij} = m_j/m$. For simplicity we assume that there are two shooting galleries visited by two groups of addicts. Our theoretical results show that the basic reproductive number R_0 is equal to the spectral radius of the matrix $\mathbf{Q}$ where it is defined by (2.17):

$$Q_{ik} = \xi \sum_{j=1}^{q} \frac{\lambda_i P_{ij} \Lambda_{kj} (1 - \phi_{kj})}{\sum_{e=1}^{p} \Lambda_{ej} + \tau_j}.$$

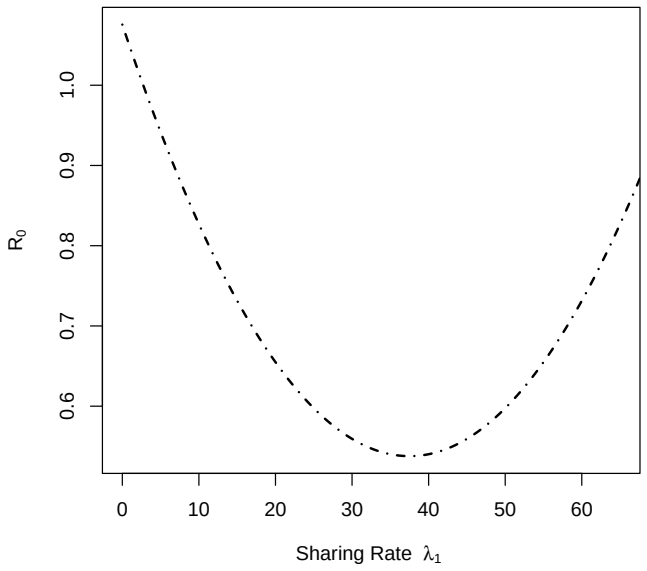


Figure 6.1: Plot presents the relationship between λ_1 and R_0 under the assumption that $P_{ij} = m_j/m$, $\phi_{ij} = \phi$. In this graph λ_1 and λ_2 are chosen to keep $\bar{\lambda}$ fixed as λ_1 varies from 0 to $n\bar{\lambda}/n_1$.

In the case where the probability P_{kj} that an addict in group k visits shooting gallery j depends only on j:

$$Q_{ik} = \xi \sum_{j=1}^{q} \left(\frac{\lambda_i P_j \lambda_k P_j \frac{n_k}{m_j}(1-\phi_{kj})}{\sum_{e=1}^{p} \Lambda_{ej} + \tau_j} \right).$$

Thus if we have $P_j = m_j/m$ for $j = 1, 2$, $\phi_{kj} = \phi$ for $j = 1, 2$ and $\tau_j = \tau$ for $j = 1, 2$:

$$Q_{ik} = \frac{\xi \lambda_i \lambda_k n_k (1-\phi) \sum_{j=1}^{2} m_j/m^2}{\frac{\lambda_1 n_1}{m} + \frac{\lambda_2 n_2}{m} + \tau},$$

so

$$R_0 \quad = \quad \rho(\boldsymbol{Q}).$$

From Lemma 2.4.1:

$$\begin{aligned} &= \sum_{i=1}^{2} Q_{ii}, \\ &= \frac{\xi(1-\phi)\left(\frac{n_1\lambda_1^2}{m} + \frac{n_2\lambda_2^2}{m}\right)}{\frac{n_1\lambda_1}{m} + \frac{n_2\lambda_2}{m} + \tau}. \end{aligned} \tag{6.1}$$

The choice of the set of sharing rates λ_i for $i = 1, 2$ to include in the numerical calculations is estimated to illustrate our theoretical results. In the first case we assume that $\lambda_1 = 65$ per year and $\lambda_2 = 10$ per year. Moreover, for simplicity we suppose that addicts' groups and shooting galleries are homogeneous in needle cleaning probability $\phi_{ij} = \phi = 0.255$ where $i, j = 1, 2$ and needle exchange rate $\tau_j = \tau = 133$ per year, $j = 1, 2$. The rest of the parameters are as we used in Chapter Three, $m_1 = m_2 = 4,491$ needles and $n_1 = n_2 = 4,500$ addicts. Thus the basic reproduction number R_0 is:

$$R_0 = \rho(\mathbf{Q}) = 0.7949.$$

Figure 6.1 illustrates the results of section 2.4 in that if the average shooting gallery visiting rate is held constant then each shooting gallery visiting rate equal to the average minimises R_0. For exterem values $\lambda_1 = 0$ or $\lambda_1 = n\bar{\lambda}/n_1$, the values of R_0 are the highest but as we move towards the minimum $\lambda_1 = \bar{\lambda} = 37.5$, the value of R_0 decreases, thus validating the original results in section 2.4. On the other hand, we will demonstrate the truth of our theoretical results by calculating R_0 under the

assumption that the sharing rate is $\bar{\lambda}$ where:

$$\bar{\lambda} = \frac{n_1\lambda_1 + n_2\lambda_2 + \cdots + n_p\lambda_p}{n_1 + n_2 + \cdots + n_p}.$$

In our case we find that $\bar{\lambda} = 37.5$ per year. Replacing λ_1 and λ_2 by $\bar{\lambda}$ and using formula (6.1) gives us that:

$$R_0 = 0.5169.$$

These results are compatible with our theoretical results as they have shown that assuming that all addicts using shooting galleries at the same rate minimises R_0.

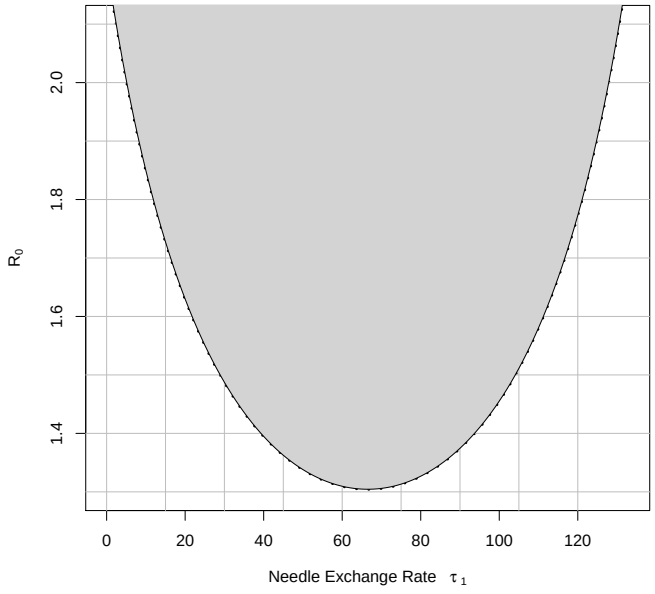


Figure 6.2: Plot presents the relationship between τ_1 and R_0 under the assumption that $\sum_{j=1}^{2} \tau_j \leq \tau$.

6.3 Numerical Results on Needle Exchange Rate

Needle exchange programmes are one of the main harm reduction measures that aim to curb the spread of blood-borne viruses such as HCV. Thus we would like to allocate a given amount of needle exchange effort to have the maximum effect. It seems reasonable to assume that this will have the most effect when R_0 is as small as possible. In order to minimise R_0, we used the Lagrange multiplier in our theoretical results by choosing $\tau_1, \tau_2, ..., \tau_q > 0$ subject to $\sum_{j=1}^{q} \tau_j \leq \tau$.

We first dealt with the situation where the needle cleaning probability ϕ_{ij} does not depend on group of addicts i or the shooting gallery j so $\phi_{ij} = \phi$ and addicts choose needles at random so that $P_{ij} = m_j/m$. The needle exchange rate τ_j depends on the shooting gallery j. The estimated parameters are $\lambda_1 = 65$ per year, $\lambda_2 = 10$ per year, $\tau = 133$ per year, $\phi = 0.225$, $\gamma = 1.002$, $n_1 = n_2 = 4,500$ addicts and $m_1 = m_2 = 4,491$ needles.

The expression of R_0 under these assumptions was found as in formula (2.29), where Figure 6.2 shows the pattern of how R_0 appears under the expression $\sum_{j=1}^{q} \tau_j \leq \tau$. Using the theoretical results in Chapter Two we find that in general R_0 is minimised when the τ_j's are not equal (i.e. $\tau_1 \neq \tau_2$) when

$$R_0 = \frac{\xi}{(\tau + q\bar{\lambda}\gamma)} \sum_{k=1}^{p} \frac{\lambda_k^2 n_k}{m} \Big[\sum_{j=1}^{q} \sqrt{\frac{m_j}{m}(1-\phi)} \Big]^2.$$

If $\tau_1 = 100$ per year and $\tau_2 = 33$ per year, so $\tau_1 + \tau_2 = 133$ per year we found that $R_0 = 1.455$ using formula (2.31) which agrees with the graph. Figure 6.3 shows

a three dimensional plot to illustrate the graph of R_0 against τ_1 and τ_2 under the assumption $\tau_1 + \tau_2 \leq \tau$. It confirms that R_0 is minimised at $\tau_1 = \tau_2 = 66.5$ per year.

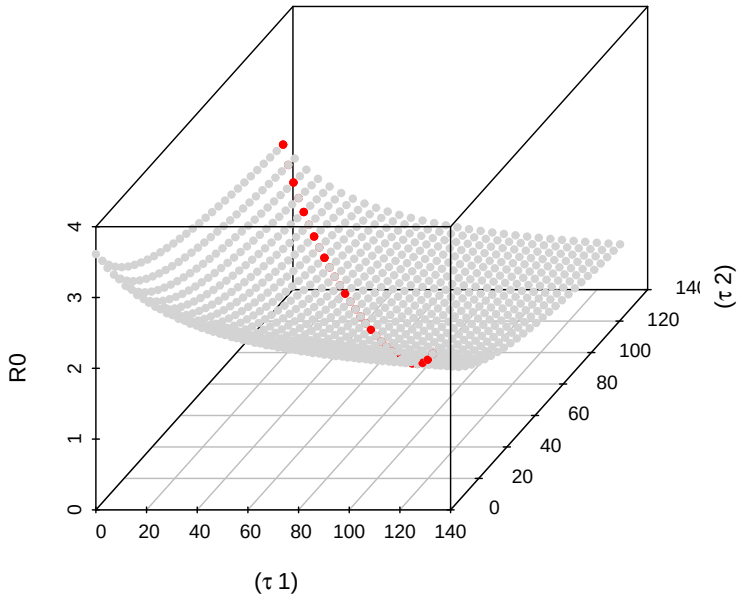


Figure 6.3: 3D plot presents the relationship between τ_1, τ_2 and R_0 under the assumption that $\sum_{j=1}^{2} \tau_j \leq \tau$. This plot was generated using `persp` in `R`.

6.4 Numerical Results on Needle Cleaning Probability

As part of our numerical results, we shall discuss the needle cleaning effort to curb the spread of HCV among drug users. Needle cleaning emerged as a solution for reducing the spread of HCV and other diseases amongst addicts. As we wish to control the disease by minimising the key threshold value we assume that the total

amount of needle cleaning effort available is Φ so that:

$$\sum_{i=1}^{p}\sum_{j=1}^{q}\phi_{ij} \leq \Phi.$$

Moreover, we assume that addicts choose needles at random, so $P_{ij} = m_j/m$, and for simplicity we also assume that the addict population is homogeneous in needle exchange rate which implies that $\tau_j = \tau$ for $j = 1, 2$. As we assumed that $p = q = 2$, our theoretical results state that under these assumptions the expression of R_0 is:

$$\begin{aligned} R_0 &= \sum_{j=1}^{2} m_j \frac{\sum_{k=1}^{2} \lambda_k^2 \frac{n_k}{m^2}\ \xi(1-\phi_{kj})}{\tau + \sum_{l=1}^{p} \lambda_l \frac{n_l}{m}}, \\ &= \sum_{j=1}^{2}\sum_{i=1}^{2} a_i\ b_j\ \xi(1-\phi_{ij}), \end{aligned} \tag{6.2}$$

where:

$$a_i = \frac{\lambda_i^2 n_i}{m^2} \qquad \text{and} \qquad b_j = \frac{m_j}{\tau + \sum_{l=1}^{p} \lambda_l \frac{n_l}{m}}.$$

To calculate R_0 and to be more biologically realistic, we assume that $m_1 \neq m_2$ and $m_1 + m_2 = m$, we take $m_1 = 3,000$ needles and $m_2 = 5,982$ needles. In our simulation we estimate $\phi = 0.255$, so we choose $\Phi = 4 \times \phi = 4 \times 0.255 = 1.02$, to make the resource greater than unity, $\Phi \geq 1$ and in this case we should use the value of the pair (i, j) which makes $a_i b_j$ the largest then apply the maximum ϕ_{ij} to reduce the value of R_0. The parameters used to calculate R_0 are estimated as: $\lambda_1 = 65$ per year, $\lambda_2 = 10$ per year, $\tau = 133$ per year and $n_1 = n_2 = 4,500$ addicts. Then we

compute the values of a_i and b_j:

$$a_1 = 0.2357 \qquad a_2 = 0.0056 \qquad b_1 = 17.588 \qquad b_2 = 35.070.$$

Thus we find that:

$$a_1b_1 = 4.1454 \qquad a_1b_2 = 8.2659 \qquad a_2b_1 = 0.0984 \qquad a_2b_2 = 0.1963.$$

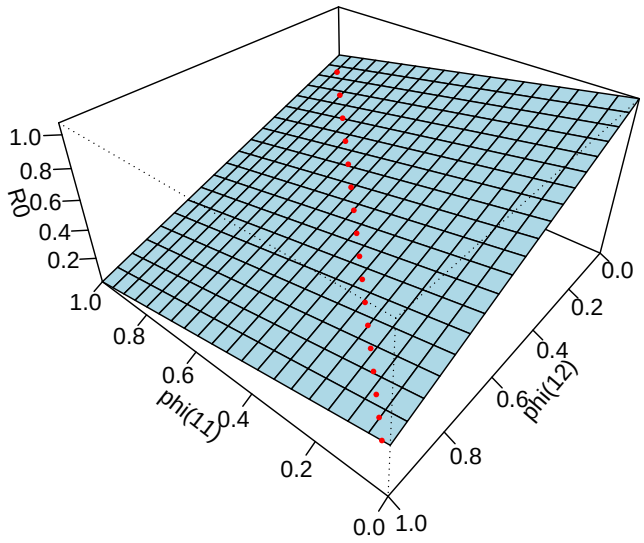


Figure 6.4: The relationship between ϕ_{11}, ϕ_{12} and R_0.

Clearly, we obtain a_1b_2 as the largest value with 8.2623 which made this pair the maximum. In order to reduce the value of R_0, we should choose the maximum value of the ϕ_{ij}'s to apply in formula (6.2). To achieve this goal we choose that $\phi_{11} = 0.02$,

$\phi_{12} = 1$ and $\phi_{21} = \phi_{22} = 0$. Hence, we calculate R_0 as:

$$R_0 = \xi\Big[a_1b_1(1-\phi_{11}) + a_1b_2(1-\phi_{12}) + a_2b_1(1-\phi_{21}) + a_2b_2(1-\phi_{22})\Big]. \qquad (6.3)$$

This gives us $R_0 = 0.3432$, which makes it the minimum value of the basic reproductive number under the effort of needle cleaning probability. The second case that we aim to discuss is that of choosing ϕ_{ij} subject to $\sum_{i=1}^{p}\sum_{j=1}^{q}\phi_{ij} \leq 1$. To illustrate that the chosen values of ϕ do indeed minimise R_0 we choose $\phi_{11} = \phi_{12} = 0.45$ and $\phi_{21} = \phi_{22} = 0.05$. Then we use equation (6.3) to calculate R_0 gives that $R_0 = 0.5976$. We conclude our discussion by presenting a three dimensional plot to express the relationship of $\phi_{11},\ \phi_{12}$ and R_0 in Figure 6.4.

6.5 Conclusion

This chapter was concerned with the numerical and simulations results of the special scenarios of R_0 which have been proved theoretically in Chapter Two. In particular, three special cases were presented:

- The effect on R_0 of addicts in different groups visiting shooting galleries at different rates.
- Optimal allocation of limited needle exchange effort between different shooting galleries.
- Optimal allocation of limited needle cleaning effort between different groups of addicts and shooting galleries.

The chapter started with the effect of variability in shooting gallery visiting rates on R_0 where we showed numerically that under the assumption that $P_{ij} = P_j$, independent of i, all addicts visiting shooting galleries at the same rate minimised R_0. These results were supported with graphs showed the relationship between R_0 and sharing rates. Then we moved to the second special scenario where we consider the optimal allocation of needle exchange as this is one of the main harm reduction measures in curbing the spread of HCV. Our numerical results showed that the calculated values of needle exchange rates to minimise the value of the basic reproductive number actually did minimise R_0.

Finally, the optimal allocation of needle cleaning effort has been discussed numerically under the assumption that the total amount of needle cleaning effort available is Φ. In this discussion, we chose the value of the pair (i, j) that makes the term $a_i b_j$ in the expression for R_0, the largest then apply the maximum possible needle cleaning effort to group i addicts using shooting gallery j to reduce the value of R_0. These values of ϕ_{ij} minimised R_0. Our results were illustrated with a graph showing the relationship between R_0 and needle cleaning probabilities. This chapter concludes our study of the basic model of the impact of heterogeneity in the spread of HCV. We shall extend this model in next chapter by consider a more realistic assumption, as we will assume that addicts can move in and out of groups and how this will affect the spread of the disease amongst addicts and needles.

Chapter 7

Extended Model: Addicts Move In and Out of Groups

In the basic mathematical model we have assumed that the number of addicts in each group n_i for $i = 1, 2 \dots p$ is constant. However in practice this assumption is not realistic as data shows that over time addicts change the rate at which they share needles. Hence, we wish to change our assumption to make our model more realistic. The objective of this chapter is to assess the spread of HCV among people who share drugs in shooting galleries and are allowed to move from group to group. Moreover, we keep all the other assumptions despite the number of addicts in each group changing. Then, we derive an expression for the basic reproductive number R_0. This is followed by analytical study of the equilibria and dynamics. We also present numerical results in the case of two groups of addicts and one shooting gallery. Numerical simulations are presented when $R_0 \leq 1$ and $R_0 > 1$.

7.1 Governing Extended Model Equations

We assume that we have p groups of addicts $i = 1, 2 \ldots p$ and that the transition rate from group i to group k is $\omega_{ik} \geq 0$. Define

$$\omega_{ii} = -\sum_{\substack{i=1 \\ k \neq i}}^{p} \omega_{ik} = -\omega_{i\bullet}.$$

Now we present the differential equation system which describes the number of addicts in each group:

$$\begin{aligned}
\frac{dn_1}{dt} &= \omega_{21}n_2 + \omega_{31}n_3 + \omega_{41}n_4 + \cdots + \omega_{p1}n_p \\
&\qquad - (\omega_{12} + \omega_{13} + \omega_{14} + \cdots + \omega_{1p})n_1, \\
\frac{dn_2}{dt} &= \omega_{12}n_1 + \omega_{32}n_3 + \omega_{42}n_4 + \cdots + \omega_{p2}n_p \\
&\qquad - (\omega_{21} + \omega_{23} + \omega_{24} + \cdots + \omega_{2p})n_2, \qquad (7.1) \\
&\vdots \qquad\qquad \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\
\frac{dn_p}{dt} &= \omega_{1p}n_1 + \omega_{2p}n_2 + \omega_{3p}n_3 + \cdots + \omega_{p-1p}n_{p-1} \\
&\qquad - (\omega_{p1} + \omega_{p2} + \omega_{p3} + \cdots + \omega_{pp-1})n_p.
\end{aligned}$$

Then let $S_{xi}, S_{x_1 i}, H_{1i}, H_{2i}, Y_i$ and Z_i denote respectively the total number of first-time susceptible individuals in group i, second and subsequent time susceptibles in group i, acutely infected h_1-class individuals in group i, acutely infected h_2-class individuals in group i, chronically infected individuals in group i and immune individuals in group i. Similarly let $B_{H_1 j}$ denote the number of needles in shooting gallery j last used by acutely infected h_1-class individuals, $B_{H_2 j}$ the number of needles in shooting

gallery j last used by acutely infected h_2-class individuals and B_{Yj} the number of needles in shooting gallery j last used by chronically infected individuals. Notice that while $B_{H_1 j}$ refers to the number of h_1 acute infectious needles in shooting gallery j, $\beta_{h_1 j}$ refers to the fractions of h_1 acute infectious needles in shooting gallery j. Thus,

$$\beta_{lj} = \frac{B_{ej}}{m_j} \qquad l = h_1, h_2, y \quad \text{and} \quad e = H_1, H_2, Y.$$

The number of group one x_1-susceptible addicts at time $t + \Delta t$:

= The number of group one x_1-susceptible addicts at time t

\+ the number of group one x_1-susceptible addicts recruited to share intravenous injecting equipments in $[t, t + \Delta t)$

\+ the number of group two x_2-susceptible addicts who move from group two to group one in $[t, t + \Delta t)$

\+ the number of group three x_3-susceptible addicts who move from group three to group one in $[t, t + \Delta t)$

\+ ...

− the number of group one x_1-susceptible addicts who leave group one to other groups in $[t, t + \Delta t)$

− the number of group one x_1-susceptible addicts who develop acute HCV infection as group one addicts choosing shooting gallery j in $[t, t + \Delta t)$

− the number of group one x_1-susceptible addicts who leave the population due cessation of injecting drug use or death in $[t, t + \Delta t)$.

Using a similar process as in the derivation of the basic model equations (2.1) - (2.9), we deduce:

$$\begin{aligned}\frac{dS_{x1}}{dt} &= \mu n_1 + \omega_{21}S_{x2} + \omega_{31}S_{x3} + \cdots + \omega_{p1}S_{xp} - (\omega_{12} + \omega_{13} + \cdots + \omega_{1p})S_{x1} \\ &\quad - \mu S_{x1} - S_{x1}\sum_{j=1}^{q}\lambda_1 P_{1j}(1-\phi_{1j})(\alpha_h(\beta_{h_1 j} + \beta_{h_2 j}) + \alpha_y\beta_{yj}). \qquad (7.2)\end{aligned}$$

It is straightforward to derive the differential equations satisfied by the quantities $S_{xi}, S_{x_1 i}, H_{1i}, H_{2i}, Y_i$ and Z_i. The right hand side of this equation is the rate of change of first time susceptible addicts in group one. The first three terms on the left hand side are the rate at which first time susceptible addicts enter group one plus the rate at which first time susceptible addicts migrate to other groups minus the rate at which first time susceptible addicts in group one migrate to other groups. The next term corresponds to the rate at which first time susceptible addicts in group one die and the last term corresponds to the rate at which these addicts become infected.

Thus in general and for $i = 1, 2, \ldots p$ the following differential equations depict the spread of HCV under the new assumption of allowing addicts to move in and out of groups:

$$\begin{aligned}\frac{dS_{xi}}{dt} &= \mu n_i + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}S_{xk} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}S_{xi} - \mu S_{xi} \\ &\quad - S_{xi}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j} + \beta_{h_2 j}) + \alpha_y\beta_{yj}\big), \qquad (7.3)\end{aligned}$$

$$\begin{aligned}
\frac{dS_{x_1i}}{dt} &= \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}S_{x_1k} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}S_{x_1i} - \mu S_{x_1i} + \sigma(1-\alpha)H_{2i} \\
&\qquad - S_{x_1i}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1j}+\beta_{h_2j}) + \alpha_y\beta_{yj}\big), \qquad (7.4)\\
\frac{dH_{1i}}{dt} &= \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}H_{1k} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}H_{1i} - (\mu+\sigma)H_{1i} \\
&\qquad + \sum_{j=1}^{q}(1-\delta)(S_{xi}+S_{x_1i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1j}+\beta_{h_2j}) + \alpha_y\beta_{yj}\big), \qquad (7.5)\\
\frac{dH_{2i}}{dt} &= \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}H_{2k} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}H_{2i} - (\mu+\sigma)H_{2i} \\
&\qquad + \sum_{j=1}^{q}\delta(S_{xi}+S_{x_1i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1j}+\beta_{h_2j}) + \alpha_y\beta_{yj}\big), \qquad (7.6)\\
\frac{dY_i}{dt} &= \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}Y_k - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}Y_i + \sigma H_{1i} - \mu Y_i, \qquad (7.7)\\
\frac{dZ_i}{dt} &= \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}Z_k - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}Z_i + \sigma\alpha H_{2i} - \mu Z_i, \qquad (7.8)\\
\frac{dB_{H_1j}}{dt} &= \sum_{i=1}^{p}\lambda_i H_{1i}P_{ij}(1-\beta_{H_1j}) - \beta_{H_1j}\sum_{i=1}^{p}\lambda_i(n_i - H_{1i})P_{ij} - \tau_j B_{H_1j}, \qquad (7.9)\\
\frac{dB_{H_2j}}{dt} &= \sum_{i=1}^{p}\lambda_i H_{2i}P_{ij}(1-\beta_{H_2j}) - \beta_{H_2j}\sum_{i=1}^{p}\lambda_i(n_i - H_{2i})P_{ij} - \tau_j B_{H_2j}, \qquad (7.10)\\
\frac{dB_{Yj}}{dt} &= \sum_{i=1}^{p}\lambda_i Y_i P_{ij}(1-\beta_{Yj}) - \beta_{Yj}\sum_{i=1}^{p}\lambda_i(n_i - Y_i)P_{ij} - \tau_j B_{Yj}. \qquad (7.11)
\end{aligned}$$

Let π_{xi} denote the fraction of first time susceptible addicts of type i at time t. Thus,

$$\pi_{xi} = \frac{S_{xi}}{n_i},$$

hence we have:

$$\begin{aligned}
\frac{d\pi_{xi}}{dt} &= \frac{\dot{S}_{xi}n_i - S_{xi}\dot{n}_i}{n_i^2}, \\
&= \frac{1}{n_i}\left(\mu n_i + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}S_{xk} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}S_{xi} - \mu S_{xi}\right) - \frac{S_{xi}}{n_i n_i}\left(\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}n_k - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}n_i\right) \\
&\quad - \frac{S_{xi}}{n_i}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big), \\
&= \mu + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{xk}\frac{n_k}{n_i} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{xi}\frac{n_k}{n_i} - \mu\pi_{xi} \\
&\quad - \pi_{xi}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big). \qquad (7.12)
\end{aligned}$$

$$\begin{aligned}
\frac{d\pi_{x_1 i}}{dt} &= \sigma(1-\alpha)\pi_{h_2 i} + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{x_1 k}\frac{n_k}{n_i} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{x_1 i}\frac{n_k}{n_i} - \mu\pi_{x_1 i} \\
&\quad - \pi_{x_1 i}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big), \qquad (7.13)
\end{aligned}$$

$$\begin{aligned}
\frac{d\pi_{h_1 i}}{dt} &= \sum_{j=1}^{q}(1-\delta)(\pi_{xi}+\pi_{x_1 i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big) \\
&\quad - (\mu+\sigma)\pi_{h_1 i} + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{h_1 k}\frac{n_k}{n_i} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{h_1 i}\frac{n_k}{n_i}, \qquad (7.14)
\end{aligned}$$

$$\begin{aligned}
\frac{d\pi_{h_2 i}}{dt} &= \sum_{j=1}^{q}\delta(\pi_{xi}+\pi_{x_1 i})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_1 j}+\beta_{h_2 j})+\alpha_y\beta_{yj}\big) \\
&\quad - (\mu+\sigma)\pi_{h_2 i} + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{h_2 k}\frac{n_k}{n_i} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{h_2 i}\frac{n_k}{n_i}, \qquad (7.15)
\end{aligned}$$

$$\frac{d\pi_{y_i}}{dt} = \sigma\pi_{h_1 i} - \mu\pi_{y_i} + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{y_k}\frac{n_k}{n_i} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{y_i}\frac{n_k}{n_i}, \qquad (7.16)$$

$$\frac{d\pi_{z_i}}{dt} = \alpha\sigma\pi_{h_2 i} - \mu\pi_{z_i} + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{z_k}\frac{n_k}{n_i} - \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\pi_{zi}\frac{n_k}{n_i}, \qquad (7.17)$$

$$\frac{d\beta_{h_1 j}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_1 i}(1-\beta_{h_1 j}) - \beta_{h_1 j}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{h_1 i}) - \tau_j\beta_{h_1 j}, \qquad (7.18)$$

$$\frac{d\beta_{h_2j}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_2i}(1-\beta_{h_2j}) - \beta_{h_2j}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{h_2i}) - \tau_j\beta_{h_2j}, \quad (7.19)$$

$$\frac{d\beta_{yj}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{yi}(1-\beta_{yj}) - \beta_{yj}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{yi}) - \tau_j\beta_{yj}, \quad (7.20)$$

with the similar suitable initial conditions: $\pi_{xi}(0), \pi_{x_1i}(0), \pi_{h_1i}(0), \pi_{h_2i}(0), \pi_{yi}(0), \pi_{zi}(0)$, $\beta_{h_1j}(0), \beta_{h_2j}(0)$ and $\beta_{yj}(0) \geq 0$ and $\pi_{xi}(0)+\pi_{x_1i}(0)+\pi_{h_1i}(0)+\pi_{h_2i}(0)+\pi_{yi}(0)+\pi_{zi}(0) = 1$. Correspondingly, $\beta_{h_1j}(0) + \beta_{h_2j}(0) + \beta_{yj}(0) \leq 1$. Next, we will discuss the basic reproductive number R_0 and give the formula which it can be calculated from.

7.2 The Basic Reproductive Number R_0

Let us recall that this number can be defined as a central quantity in the investigation and management of infectious disease (Dietz, 1993). Note that both the basic model and the extended model have the same disease-free equilibrium (DFE), namely $\pi_{xi} = 1$ for $i = 1, 2, \ldots p$ and $\pi_{x_1i} = \pi_{h_1i} = \pi_{h_2i} = \pi_{yi} = \pi_{zi} = 0$ for $i = 1, 2, \ldots p$ and $\beta_{h_1j} = \beta_{h_2j} = \beta_{yj} = 0$ for $j = 1, 2, \ldots q$. Hence to derive R_0 in the extended model, the infection scenario can be divided into two stages:

1. The infected addict passes the infection to uninfected needles.

2. The newly infected needles then infect susceptible addicts.

We start with the simplest case to understand and derive R_0 for the two groups case ($p = 2$). Then we move to more general case where we have p groups of addicts. Under the assumption that addicts move in and out of groups we shall present an expression of R_0, which determines the general behaviour of the extended model.

Derivation of R_0 in the 2×2 Case

Assume that we have only two groups where addicts can move between groups. As infected addict in one group passes the infection to uninfected needles in one of the shooting galleries, then the newly infected needles (at any stage of infectivity) infect susceptible addicts in both groups.

Now we consider a single newly infected addict in group one entering a disease-free population containing only susceptible addicts and needles. This newly infected addict enters the acute h_{11} stage with probability $(1 - \delta)$. By our assumption all rates are constant, this means that the expected duration (time) of infection is the inverse of the removal rate. Thus, each infected addict in group one shares injecting needles from group one for an average $1/(\mu + \sigma + \omega_{12})$ time units before the next event. During this time he or she uses needles at rate λ_1 and chooses the shooting gallery j with probability P_{1j}. They then progress to the chronic stage of infection with probability $\sigma/(\mu + \sigma + \omega_{12})$ where they remain for an average $1/\mu$ time units. In the chronic stage of infection, the addicts may jump from group one to two or from group two to one many times before they leave the population. The second possibility is that at the end of the period of injecting in group one the addict stops sharing. This happens with probability $\mu/(\mu + \sigma + \omega_{12})$.

The third possibility is that after the end of this period of injecting in group one, the group one h_{11} addict moves to group two with probability $\omega_{12}/(\mu+\sigma+\omega_{12})$. For the purposes of calculation of the basic reproductive number we regard this as

producing a newly infected h_{11} addict in group two (directly without any needles being infected).

On initial infection our group one infected addict can also move into the acute stage h_{21} with probability δ. They remain there for an average $1/(\mu+\sigma+\omega_{12})$ time units until the next event happens. After, there are two stages which addicts can progress to, the immune stage with probability $\sigma\alpha/(\mu+\sigma+\omega_{12})$ and they remain for an average $1/\mu$ time units, or the x_{11}-susceptible stage with probability $\sigma(1-\alpha)/(\mu+\sigma+\omega_{12})$ where they remain for an average $1/\mu$ time units, otherwise they leave the population or switch group.

An h_{21} addict who enters either the immune class or the x_{11}-susceptible class produces no more infected needles. At the end of the first period of injecting in group one the h_{21} infected addict may also switch to group two with probability $\omega_{12}/(\mu+\sigma+\omega_{12})$ and as in the h_{11} case we regard this as directly producing a newly infected h_{21} addict in group two. Hence, in total a single newly infected addict in group one causes on average:

$$\frac{\lambda_1 P_{1j}(1-\delta)}{\mu+\sigma+\omega_{12}} \quad \text{acute } h_{1j} \text{ infectious needles,}$$

and

$$\frac{\lambda_1 P_{1j}\delta}{\mu+\sigma+\omega_{12}} \quad \text{acute } h_{2j} \text{ infectious needles.}$$

We shall next find the total number of infectious needles in stage y_j $(j=1,2,\ldots q)$, caused by this addict. Immediately after entering state y the addict is still in group one. The next event (either leaving the population or switching groups) occurs after

time $1/(\mu+\omega_{12})$ and during this time the addict infects:

$$\frac{\sigma}{(\mu+\sigma+\omega_{12})}\frac{\lambda_1 P_{1j}(1-\delta)}{(\mu+\omega_{12})},$$

state y needles in group j. If the next event is leaving the sharing injecting population no more needles are infected. However with probability $\omega_{12}/(\mu+\omega_{12})$ the next event is that the addict switches to group two when the expected number of state y needles in shooting gallery j between the first and second events is:

$$\frac{\sigma}{(\mu+\sigma+\omega_{12})}\frac{\omega_{12}}{(\mu+\omega_{12})}\frac{\lambda_2 P_{2j}(1-\delta)}{(\mu+\omega_{21})}.$$

The third event can then be either leaving the sharing, injecting population or jumping back to group one. The latter occurs with probability $\omega_{21}/(\mu+\omega_{21})$ and after this before the next event the addict will infect an expected number

$$\frac{\sigma}{(\mu+\sigma+\omega_{12})}\frac{\omega_{12}\omega_{21}}{(\mu+\omega_{12})(\mu+\omega_{21})}\frac{\lambda_1 P_{1j}(1-\delta)}{(\mu+\omega_{12})},$$

more state y needles in shooting gallery j. The addict can jump between the groups many times before leaving the sharing injecting population. So the total number state y shooting gallery j infected needles is:

$$\frac{\sigma}{\mu+\sigma+\omega_{12}}\left[\frac{\lambda_1 P_{1j}(1-\delta)}{\mu+\omega_{12}}\left(1+\frac{\omega_{12}\omega_{21}}{(\mu+\omega_{12})(\mu+\omega_{21})}+\frac{\omega_{12}^2\omega_{21}^2}{(\mu+\omega_{12})^2(\mu+\omega_{21})^2}+\ldots\right)\right.$$
$$\left.+\frac{\omega_{12}}{(\mu+\omega_{12})}\frac{\lambda_2 P_{2j}(1-\delta)}{\mu+\omega_{21}}\left(1+\frac{\omega_{12}\omega_{21}}{(\mu+\omega_{12})(\mu+\omega_{21})}+\ldots\right)\right].$$

Using the definition of the geometric series, we rewrite this as:

$$
\begin{aligned}
&= \frac{\sigma}{(\mu+\sigma+\omega_{12})}\left[\frac{\lambda_1 P_{1j}(1-\delta)}{(\mu+\omega_{12})}\frac{1}{\left(1-\frac{\omega_{12}\omega_{21}}{(\mu+\omega_{12})(\mu+\omega_{21})}\right)}\right. \\
&\qquad\qquad \left. + \frac{\omega_{12}}{(\mu+\omega_{12})}\frac{\lambda_2 P_{2j}(1-\delta)}{(\mu+\omega_{21})}\frac{1}{\left(1-\frac{\omega_{12}\omega_{21}}{(\mu+\omega_{12})(\mu+\omega_{21})}\right)}\right], \\
&= \frac{\sigma}{\mu+\sigma+\omega_{12}}\left[\frac{\lambda_1 P_{1j}(1-\delta)(\mu+\omega_{21})}{\mu(\mu+\omega_{12}+\omega_{21})} + \frac{\lambda_2 P_{2j}(1-\delta)\omega_{12}}{\mu(\mu+\omega_{12}+\omega_{21})}\right], \\
&= \frac{\sigma(1-\delta)\Big[\lambda_1 P_{1j}(\mu+\omega_{21}) + \lambda_2 P_{2j}\omega_{12}\Big]}{\mu(\mu+\sigma+\omega_{12})(\mu+\omega_{12}+\omega_{21})}. \qquad (7.21)
\end{aligned}
$$

We have thus derived the number of each type of infected needle caused by the original group one infected addict in shooting gallery j. We assume that these newly infected needles will be used by uninfected addicts in the two groups. Thus, we aim to derive the expected number of these addicts in group k infected by these newly infected needles. Note that needles are not assumed to move from one shooting gallery to another, thus we use a similar argument as in our basic model to derive the expected number of addicts that are infected by acute h_{1j} needles until they are not infectious and obtain that the acute h_{1j} needle is infected for $1/(\sum_{k=1}^{p}\Lambda_{kj}+\tau_j)$ time units. During this time it infects:

$$
\frac{\Lambda_{kj}(1-\phi_{kj})\alpha_h}{(\sum_{k=1}^{p}\Lambda_{kj}+\tau_j)} \qquad \text{addicts in group } k. \qquad (7.22)
$$

Similarly, a single needle last used and infected by an addict in class h_{2j} entering a disease-free population at equilibrium infects:

$$\frac{\Lambda_{kj}(1-\phi_{kj})\alpha_h}{(\sum_{k=1}^{p}\Lambda_{kj}+\tau_j)} \qquad \text{addicts in group } k, \tag{7.23}$$

and a single needle last used and infected by an addict in class y_j entering a disease-free population at equilibrium infects:

$$\frac{\Lambda_{kj}(1-\phi_{kj})\alpha_y}{(\sum_{k=1}^{p}\Lambda_{kj}+\tau_j)} \qquad \text{addicts in group } k. \tag{7.24}$$

Thus, Q_{11}, the total expected number of secondary addicts in group one left infected by a single newly infected addict entering group one is the sum of those infected by h_{1j} needles plus the sum of those infected by h_{2j} needles plus the sum of those infected via y_j needles. In the expression for Q_{12} there is an extra term corresponding to the first event being the original h_{11} or h_{21} infected addict jumping directly to group two. So:

$$\begin{aligned} Q_{1k} \;=\; & \sum_{j=1}^{q}\frac{\Lambda_{kj}(1-\phi_{kj})}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\left[\frac{\alpha_h\lambda_1 P_{1j}}{\mu+\sigma+\omega_{12}}+\frac{\alpha_y(1-\delta)\sigma}{\mu+\sigma+\omega_{12}}\left[\frac{\lambda_1 P_{1j}(\mu+\omega_{21})}{\mu(\mu+\omega_{12}+\omega_{21})}\right.\right. \\ & \left.\left.+\frac{\lambda_2 P_{2j}\omega_{12}}{\mu(\mu+\omega_{12}+\omega_{21})}\right]\right]+I(k=2)\frac{\omega_{12}}{\mu+\sigma+\omega_{12}}, \end{aligned} \tag{7.25}$$

where

$$I(k=2)=\begin{cases} 1 & \text{if } k=2, \\ 0 & \text{otherwise.} \end{cases}$$

Similarly, Q_{2k}, the total expected number of secondary addicts in group k left infected by a single newly infected addict entering group two is:

$$Q_{2k} = \sum_{j=1}^{q} \frac{\Lambda_{kj}(1-\phi_{kj})}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\left[\frac{\alpha_h\lambda_2 P_{2j}}{\mu+\sigma+\omega_{21}} + \frac{\alpha_y(1-\delta)\sigma}{\mu+\sigma+\omega_{21}}\left[\frac{\lambda_2 P_{2j}(\mu+\omega_{12})}{\mu(\mu+\omega_{12}+\omega_{21})}\right.\right.$$
$$\left.\left. + \frac{\lambda_1 P_{1j}\omega_{21}}{\mu(\mu+\omega_{12}+\omega_{21})}\right]\right] + I(k=1)\frac{\omega_{21}}{\mu+\sigma+\omega_{21}}. \tag{7.26}$$

Thus R_0 is the spectral radius of the matrix $\boldsymbol{Q}$. In next section, we shall look at the more general case where we have more than two groups.

Derivation of R_0 in the $p \times p$ Case

Now if we have p groups where addicts move between groups, how do we derive R_0 in this case? Let us consider a single newly infected addict of group i entering a disease-free equilibrium population. Following a similar argument we find the number of newly infected needles in shooting gallery j are:

$$\frac{\lambda_i P_{ij}(1-\delta)}{\mu+\sigma+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}} \qquad \text{acute } h_{1j} \text{ infectious needles,}$$

$$\frac{\lambda_i P_{ij}\delta}{\mu+\sigma+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}} \qquad \text{acute } h_{2j} \text{ infectious needles.}$$

Similarly we find the number of infectious needles in stage y_j caused by a single newly infected addict entering group i is:

$$\frac{\sigma(1-\delta)}{\left(\mu+\sigma+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)}\left[\frac{\lambda_i P_{ij}}{\left(\mu+\sum_{\substack{k_2=1\\k_2\neq i}}^{p}\omega_{ik_2}\right)}+\sum_{\substack{l_2=1\\l_2\neq i}}^{p}\frac{\omega_{il_2}\lambda_{l_2}P_{l_2j}}{\left(\mu+\sum_{\substack{k_2=1\\k_2\neq i}}^{p}\omega_{ik_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l_2}}^{p}\omega_{l_2k_3}\right)}\right.$$
$$\left.+\sum_{\substack{l_2=1\\l_2\neq i}}^{p}\sum_{\substack{l_3=1\\l_3\neq k_2}}^{p}\frac{\omega_{il_2}\omega_{l_2l_3}\lambda_{l_3}P_{l_3j}}{\left(\mu+\sum_{\substack{k_2=1\\k_2\neq i}}^{p}\omega_{ik_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l_2}}^{p}\omega_{l_2k_3}\right)\left(\mu+\sum_{\substack{k_4=1\\k_4\neq l_3}}^{p}\omega_{l_3k_4}\right)}+\ldots\right].$$

Thus, the total expected number of secondary addicts in group k caused by a single newly infected addict of group i entering the population at equilibrium is:

$$\begin{aligned}Q_{ik} &= \sum_{j=1}^{q}\frac{\Lambda_{kj}(1-\phi_{kj})}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\left[\frac{\alpha_h\lambda_i P_{ij}}{\mu+\sigma+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}}+\frac{\alpha_y\sigma(1-\delta)}{\mu+\sigma+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}}\left[\frac{\lambda_i P_{ij}}{\mu+\sum_{\substack{k_2=1\\k_2\neq i}}^{p}\omega_{ik_2}}\right.\right.\\
&\quad+\sum_{\substack{l_2=1\\l_2\neq i}}^{p}\frac{\omega_{il_2}\lambda_{l_2}P_{l_2j}}{\left(\mu+\sum_{\substack{k_2=1\\k_2\neq i}}^{p}\omega_{ik_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l_2}}^{p}\omega_{l_2k_3}\right)}\\
&\quad\left.\left.+\sum_{\substack{l_2=1\\l_2\neq i}}^{p}\sum_{\substack{l_3=1\\l_3\neq l_2}}^{p}\frac{\omega_{il_2}\omega_{l_2l_3}\lambda_{l_3}P_{l_3j}}{\left(\mu+\sum_{\substack{k_2=1\\k_2\neq i}}^{p}\omega_{ik_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l_2}}^{p}\omega_{l_2k_3}\right)\left(\mu+\sum_{\substack{k_4=1\\k_4\neq l_3}}^{p}\omega_{l_3k_4}\right)}+\ldots\right]\right]\\
&\quad+\frac{\omega_{ik}}{\mu+\sigma+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}}I(k\neq i).\end{aligned}\tag{7.27}$$

Here

$$I(k\neq i)=\begin{cases}1 & \text{if } k\neq i,\\ 0 & \text{if } k=i.\end{cases}$$

Note that R_0 is the spectral radius of the $p\times p$ matrix $\mathbf{Q}$. We now examine the behaviour of the model analytically and dynamically. In particular, we are interested in the conditions that allow HCV to die out or persist in the population.

7.3 Analysis of Group Size Dynamics

We are interested in analysing the dynamical system of differential equations which describe the spread of the disease amongst addicts who move in and out of groups, but before we do this we need to understand the dynamics of the groups themselves. Please note that the equations which describe how addicts move in and out of groups are described by the system (7.1):

$$\begin{aligned}
\frac{dn_1}{dt} &= \omega_{21}n_2 + \omega_{31}n_3 + \omega_{41}n_4 + \cdots + \omega_{p1}n_p - (\omega_{12} + \omega_{13} + \omega_{14} + \cdots + \omega_{1p})n_1, \\
\frac{dn_2}{dt} &= \omega_{12}n_1 + \omega_{32}n_3 + \omega_{42}n_4 + \cdots + \omega_{p2}n_p - (\omega_{21} + \omega_{23} + \omega_{24} + \cdots + \omega_{2p})n_2, \\
\frac{dn_3}{dt} &= \omega_{13}n_1 + \omega_{23}n_3 + \omega_{43}n_4 + \cdots + \omega_{p3}n_p - (\omega_{31} + \omega_{32} + \omega_{34} + \cdots + \omega_{3p})n_3, \\
\vdots \quad & \qquad \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\
\frac{dn_p}{dt} &= \omega_{1p}n_1 + \omega_{2p}n_2 + \omega_{3p}n_3 + \cdots + \omega_{p-1p}n_{p-1} \\
&\qquad\qquad - (\omega_{p1} + \omega_{p2} + \omega_{p3} + \cdots + \omega_{pp-1})n_p,
\end{aligned}$$

with suitable initial conditions. Our main result in this section is proving that the above system of differential equations has a unique globally stable equilibrium.

The result is split into two halves. The first theorem will show that there is a unique positive equilibrium distribution and the second that the system of group size dynamic interaction (7.1) tends to that unique equilibrium distribution.

In order to analyse our dynamical group size system, we use *continuous time Markov Chain* (CTMC) processes. These processes can be described as probabilistic models for describing data with a sequential structure, where the state evolves over time (Gardiner, 1985). In this work, we consider Markov processes that are homogeneous in time and have a finite state space. This will enable us to use established theorems on convergence of ergodic Markov Chains to their equilibrium distributions without proving the results ourselves. The dynamics of the process are described by the initial conditions and by a rate matrix $\mathbf{Q} = (\omega_{ik})$, whose off-diagonal entries ω_{ik} are exponential rate intensities for transition from state i to state k.

Let us consider a p-dimensional Markov process with transition rate from state i to state k, being ω_{ik}. In our extended model, addicts are assumed to move from group i to group k with rate ω_{ik}. If $i \neq k$ then $\omega_{ik} > 0$ and if $i = k$:

$$\omega_{ii} = -\sum_{\substack{k=1 \\ k \neq i}}^{p} \omega_{ik} = -\omega_{i\bullet}.$$

We denote the $p \times p$ matrix of moving rates by $\mathbf{Q} = (\omega_{ik})$. Let $X(t)$ be the random variable describing the state of the process at time t, and also assume that the process is in state (i.e. group) i at time t_0. The dynamics of a continuous-time Markov process are fully determined by the *Markov transition function*:

$$P_{ik}(t) = Pr(X(t) = k | X(t_0) = i). \tag{7.28}$$

The matrix $\mathbf{P}(t)$ with entries $P_{ik}(t)$ satisfies the matrix differential equation

$$\frac{d\mathbf{P}}{dt} = \mathbf{P}(t)\mathbf{Q}, \tag{7.29}$$

in other words

$$\frac{dP_{ik}}{dt} = \sum_{m=1}^{p} P_{im}(t)\ Q_{mk}, \qquad\qquad i,k = 1,2,\ldots p, \tag{7.30}$$

with initial condition $\mathbf{P}(0) = \mathbf{I}$, where $\mathbf{I}$ is the $p \times p$ identity matrix. The general solution for the equation (7.30) is given by:

$$\mathbf{P}(t) = e^{\mathbf{Q}t}, \tag{7.31}$$

where $e^{\mathbf{Q}t}$ is the matrix exponential defined by the *Taylor series*:

$$e^{\mathbf{Q}t} = \sum_{k=0}^{\infty} \frac{(\mathbf{Q}t)^k}{k!}. \tag{7.32}$$

If the Markov process is representing a single individual in state i, where $i = 1,2,\ldots p$, then consequently if initially we have a collection of $n_1(0) + n_2(0) + \cdots + n_p(0)$ individuals whose distribution between the groups is $(n_1(0), n_2(0), \ldots, n_p(0))$, then the number of addicts in group k at time t is:

$$n_k(t) \quad = \quad n_1(0)P_{1k}(t) + n_2(0)P_{2k}(t) + \cdots + n_p(0)P_{pk}(t),$$

$$= \quad \Big(P_{1k}(t), P_{2k}(t), \ldots, P_{pk}(t)\Big) \times \begin{pmatrix} n_1(0) \\ n_2(0) \\ \vdots \\ n_p(0) \end{pmatrix},$$

using (7.31):

$$\begin{pmatrix} n_1 \\ n_2 \\ \vdots \\ n_p \end{pmatrix} \quad = \quad e^{\mathbf{Q}^T t} \begin{pmatrix} n_1(0) \\ n_2(0) \\ \vdots \\ n_p(0) \end{pmatrix}.$$

So differentiating with respect to t:

$$\frac{d}{dt}\begin{pmatrix} n_1 \\ n_2 \\ \vdots \\ n_p \end{pmatrix} \quad = \quad \mathbf{Q}^T \begin{pmatrix} n_1 \\ n_2 \\ \vdots \\ n_p \end{pmatrix},$$

$$= \begin{pmatrix} -\omega_{1\bullet} & \omega_{21} & \ldots & \omega_{p1} \\ \omega_{12} & -\omega_{2\bullet} & \ldots & \omega_{p2} \\ \vdots & \vdots & \ddots & \vdots \\ \omega_{1p} & \omega_{2p} & \ldots & -\omega_{p\bullet} \end{pmatrix} \times \begin{pmatrix} n_1 \\ n_2 \\ \vdots \\ n_p \end{pmatrix}. \qquad (7.33)$$

We will start addressing the task by assuming that we have p groups of addicts $i = 1, 2, \ldots p$ and that the transition rate from group i to group k is $\omega_{ik} \geq 0$ for each i and k, and that, for M a sufficiently large constant, the matrix $(\mathbf{Q} + M\mathbf{I})$

is irreducible. Now, we can present the differential equations system which describe the number of addicts in each group:

$$\begin{aligned}
\frac{dn_1}{dt} &= \omega_{21}n_2 + \omega_{31}n_3 + \omega_{41}n_4 + \cdots + \omega_{p1}n_p - (\omega_{12} + \omega_{13} + \omega_{14} + \cdots + \omega_{1p})n_1, \\
\frac{dn_2}{dt} &= \omega_{12}n_1 + \omega_{32}n_3 + \omega_{42}n_4 + \cdots + \omega_{p2}n_p - (\omega_{21} + \omega_{23} + \omega_{24} + \cdots + \omega_{2p})n_2, \\
\\
\frac{dn_3}{dt} &= \omega_{13}n_1 + \omega_{23}n_2 + \omega_{43}n_4 + \cdots + \omega_{p3}n_p - (\omega_{31} + \omega_{32} + \omega_{34} + \cdots + \omega_{3p})n_3, \\
\vdots &\qquad\qquad \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\
\frac{dn_p}{dt} &= \omega_{1p}n_1 + \omega_{2p}n_2 + \omega_{3p}n_3 + \cdots + \omega_{p-1}n_{p-1} \\
&\qquad\qquad - (\omega_{p1} + \omega_{p2} + \omega_{p3} + \cdots + \omega_{pp-1})n_p,
\end{aligned} \tag{7.34}$$

which are the same equations that we described above (equations 7.33). We will use the probability that an addict is in group k at time t, so that:

$$\begin{aligned}
\bar{P}_k &= \frac{n_k}{n}, \\
\bar{P}_k(t) &= \sum_{i=1}^{p} \bar{P}_i(0) P_{ik}(t).
\end{aligned} \tag{7.35}$$

Then by differentiating equation (7.35) we deduce that:

$$\begin{aligned}
\frac{d\bar{P}_1}{dt} &= \omega_{21}\bar{P}_2 + \omega_{31}\bar{P}_3 + \omega_{41}\bar{P}_4 + \cdots + \omega_{p1}\bar{P}_p - (\omega_{12} + \omega_{13} + \omega_{14} + \cdots + \omega_{1p})\bar{P}_1, \\
\frac{d\bar{P}_2}{dt} &= \omega_{12}\bar{P}_1 + \omega_{32}\bar{P}_3 + \omega_{42}\bar{P}_4 + \cdots + \omega_{p2}\bar{P}_p - (\omega_{21} + \omega_{23} + \omega_{24} + \cdots + \omega_{2p})\bar{P}_2, \\
\frac{d\bar{P}_3}{dt} &= \omega_{13}\bar{P}_1 + \omega_{23}\bar{P}_2 + \omega_{43}\bar{P}_4 + \cdots + \omega_{p3}\bar{P}_p - (\omega_{31} + \omega_{32} + \omega_{34} + \cdots + \omega_{3p})\bar{P}_3, \\
\vdots &\qquad\qquad \vdots \qquad\qquad \vdots \qquad\qquad \vdots
\end{aligned} \tag{7.36}$$

$$\frac{d\bar{P}_p}{dt} = \omega_{1p}\bar{P}_1 + \omega_{2p}\bar{P}_2 + \omega_{3p}\bar{P}_3 + \cdots + \omega_{p-1}\bar{P}_{p-1} - (\omega_{p1} + \omega_{p2} + \omega_{p3} + \cdots + \omega_{pp-1})\bar{P}_p.$$

Obviously, from equation (7.30) and $\bar{P}_k(t) = \sum_{i=1}^{p} \bar{P}_i(0)P_{ik}(t)$ we can rewrite (7.36) as:

$$\frac{d\bar{P}_k}{dt} = \sum_{m=1}^{p} \bar{P}_m(t)Q_{mk}.$$

This completes our mathematical preliminaries giving the background to the problem. We have shown how the system of differential equations (7.34) describing the number of addicts in each group can be regarded as an aggregate of individual processes representing individuals (or addicts) whose dynamics are given by the Markov transition function $P_{ik}(t)$. We shall use this more basic interpretation of the model to prove our two main results of this section.

The first principal result of this section is the following theorem:

Theorem 7.3.1. *There is a unique positive equilibrium solution to equation (7.34) for the addict group sizes.*

Proof. We begin by observing that the p-dimensional vector $\mathbf{1} = (1, 1, \ldots, 1)^T$ is obviously a right eigenvector of the matrix $\mathbf{Q}$ with the eigenvalue $\lambda = 0$. Thus, if M is large enough, then $(\mathbf{Q} + M\mathbf{I})$ is a matrix with strictly positive entries and M is an eigenvalue of the matrix with positive eigenvector $\mathbf{1}$.

Since $(\mathbf{Q} + M\mathbf{I})$ is an irreducible matrix (with positive off-diagonal elements),

the *Perron-Frobenius* theorem for irreducible matrices (Lancaster & Tismenetsky, 1969) implies that M is a simple eigenvalue of the matrix $(\mathbf{Q} + M\mathbf{I})$ and equal to its spectral radius. Hence $\lambda = 0$ is a simple eigenvalue of the matrix $\mathbf{Q}$ and all other eigenvalues have strictly negative real parts. Moreover, M is also a simple eigenvalue of the matrix $(\mathbf{Q}^T + M\mathbf{I})$ with strictly positive right eigenvector $\boldsymbol{\pi}^T$ where:

$$\boldsymbol{\pi}^T = (\pi_1, \pi_2, \ldots, \pi_p)^T \qquad \pi_i > 0 \qquad \text{for} \quad i = 1, 2, \ldots, p,$$

and without loss of generality we may assume that:

$$\pi_1 + \pi_2 + \cdots + \pi_p = 1. \tag{7.37}$$

It follows that $\lambda = 0$ is a simple eigenvalue of the matrix $\mathbf{Q}^T$ with right eigenvector $(\pi_1, \pi_2, \ldots, \pi_p)^T$. Thus, $\boldsymbol{\pi}$ can be regarded as an equilibrium probability distribution for the state of an individual addict and considering equation (7.33):

$$n' = n(\pi_1, \pi_2, \ldots, \pi_p)^T, \tag{7.38}$$

is an equilibrium distribution for n.

To examine the uniqueness of the equilibrium distribution n' suppose that we have another equilibrium distribution $\tilde{n}$ which is defined as:

$$\tilde{n} = (\tilde{n}_1, \tilde{n}_2, \ldots, \tilde{n}_p)^T, \tag{7.39}$$

where $\sum_{i=1}^{p} \tilde{n}_i = \sum_{i=1}^{p} n_i(0) = n$. Define the vector $\tilde{\boldsymbol{\pi}}$ by:

$$\tilde{\boldsymbol{\pi}} = (\tilde{\pi}_1, \tilde{\pi}_2, \ldots, \tilde{\pi}_p),$$

where:

$$\tilde{\pi}_i = \frac{\tilde{n}_i}{n} \qquad \text{for} \quad i = 1, 2, \ldots p.$$

Note that $\sum_{i=1}^{p} \tilde{\pi}_i = 1$, and also:

$$\mathbf{Q}^T \tilde{\boldsymbol{\pi}}^T = \mathbf{0}.$$

We deduce that $\tilde{\boldsymbol{\pi}}^T$ is a right eigenvector of the matrix $\mathbf{Q}^T$ with eigenvalue $\lambda = 0$. It follows that:

$$\tilde{\boldsymbol{\pi}}^T = K \boldsymbol{\pi}^T,$$

since the corresponding eigenspace has one dimension. However, we assumed that the sum of the components of $\tilde{\pi}$ equals unity in the formula (7.37) which leads to:

$$\sum_{i=1}^{p} \tilde{\pi}_i = \sum_{i=1}^{p} \pi_i = 1,$$

which implies that $K = 1$, and therefore $\tilde{\boldsymbol{\pi}} = \boldsymbol{\pi}$. Thus $\boldsymbol{\pi}$, the equilibrium probability distribution for the state of a single addict, is unique, consequently $n\boldsymbol{\pi}$ which represents the equilibrium solution of group sizes in our group size dynamic model (7.34) is also unique and these results proved this theorem. □

So far we have answered an important question of whether the equilibrium size distribution of our addict group size dynamic model is unique, which means that no

multiple equilibria are possible. This leads us to another important point about the development of our group dynamic model over time. The following theorem states and discusses this point.

Theorem 7.3.2. *The system of our addict group size dynamic model (7.34) approaches the unique equilibrium as time becomes large.*

Proof. The dynamics of a CTMC process are fully determined by the Markov transition function (7.28). In order to prove this theorem, we consider the CTMC process and two cases shall be considered:

- Case one is of size 2×2.
- Case two is of size $p \times p$.

(i) The 2×2 Case:

For simplicity we shall start with the first case where $p = 2$. The $\mathbf{Q}$ matrix can be expressed as:

$$\mathbf{Q} = \begin{bmatrix} -\alpha & \alpha \\ \beta & -\beta \end{bmatrix} \tag{7.40}$$

with eigenvalues $\lambda_1 = 0$ and $\lambda_2 = -(\alpha + \beta)$. We have that the left eigenvector of the matrix $\mathbf{Q}$ corresponding to the eigenvalue $\lambda_1 = 0$ is:

$$\mathbf{e}_1 = \Big(\frac{\beta}{\alpha+\beta}, \frac{\alpha}{\alpha+\beta}\Big),$$

and we have assumed that $e_{11} + e_{12} = 1$. Moreover, the left eigenvector of the matrix $\mathbf{Q}$ corresponding to the eigenvalue $\lambda_2 = -(\alpha + \beta)$ is $\mathbf{e}_2 = (1, -1)$ with a negative component. Suppose that $\mathbf{E}$ is a matrix with rows consisting of these 2 independent

eigenvectors $\mathbf{e}$ of the matrix $\mathbf{Q}$:

$$\mathbf{E} = \begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \end{bmatrix}.$$

Thus we have:

$$\mathbf{E} \;=\; \begin{bmatrix} e_{11} & e_{12} \\ e_{21} & e_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ 1 & -1 \end{bmatrix}.$$

Since all vectors $\mathbf{e}_i$ are linearly independent, the matrix $\mathbf{E}$ is non-singular and

$$\mathbf{E}\ \mathbf{Q}\ \mathbf{E^{-1}} = \mathbf{J}.$$

The Jordan normal form of a square $p \times p$ matrix $\mathbf{Q}$ with unique eigenvalues $\lambda_1, \lambda_2, \ldots, \lambda_p$ is the square $p \times p$ diagonal matrix $\mathbf{J}$ where:

$$\mathbf{J} \;=\; \begin{bmatrix} \lambda_1 & 0 & \ldots & 0 \\ 0 & \lambda_2 & & \vdots \\ \vdots & \ddots & & \vdots \\ 0 & \ldots & 0 & \lambda_p \end{bmatrix}.$$

Thus here:

$$\mathbf{J} \;=\; \begin{bmatrix} 0 & 0 \\ 0 & -(\alpha+\beta) \end{bmatrix}.$$

It is easy to check that:

$$\mathbf{E}^{-1} = \begin{bmatrix} 1 & \frac{\alpha}{\alpha+\beta} \\ 1 & -\frac{\beta}{\alpha+\beta} \end{bmatrix}.$$

Now, we shall compute the matrix $\mathbf{EQE}^{-1}$:

$$\begin{aligned} \mathbf{EQE}^{-1} &= \begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ 1 & -1 \end{bmatrix} \begin{bmatrix} -\alpha & \alpha \\ \beta & -\beta \end{bmatrix} \begin{bmatrix} 1 & \frac{\alpha}{\alpha+\beta} \\ 1 & -\frac{\beta}{\alpha+\beta} \end{bmatrix}, \\ &= \begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ 1 & -1 \end{bmatrix} \begin{bmatrix} 0 & -\alpha \\ 0 & \beta \end{bmatrix}, \\ &= \begin{bmatrix} 0 & 0 \\ 0 & -(\alpha+\beta) \end{bmatrix}. \end{aligned}$$

Hence we have checked that $\mathbf{EQE}^{-1} = \mathbf{J}$, and therefore we deduce that:

$$\mathbf{Q} = \mathbf{E}^{-1}\mathbf{JE}.$$

Using this expression $\mathbf{Q} = \mathbf{E}^{-1}\mathbf{JE}$ and from formula (7.32) we can write:

$$\begin{aligned} e^{\mathbf{Q}t} &= \sum_{k=0}^{\infty} \frac{(\mathbf{Q}t)^k}{k!}, \\ &= \sum_{k=0}^{\infty} \frac{1}{k!}\Big(\mathbf{E}^{-1}\mathbf{J}t\mathbf{E}\Big)^k, \\ &= \mathbf{E}^{-1}\left(\sum_{k=0}^{\infty} \frac{(\mathbf{J}t)^k}{k!}\right)\mathbf{E}, \\ &= \mathbf{E}^{-1}e^{\mathbf{J}t}\mathbf{E}. \end{aligned}$$

Thus we deduce that:

$$\begin{aligned}
e^{\mathbf{Q}t} &= \mathbf{E}^{-1}\begin{bmatrix} e^{\lambda_1 t} & 0 \\ 0 & e^{\lambda_2 t} \end{bmatrix}\mathbf{E}, \\
&= \mathbf{E}^{-1}\begin{bmatrix} 1 & 0 \\ 0 & e^{-(\alpha+\beta)t} \end{bmatrix}\mathbf{E}, \\
&= \begin{bmatrix} 1 & \frac{\alpha}{\alpha+\beta} \\ 1 & -\frac{\beta}{\alpha+\beta} \end{bmatrix}\begin{bmatrix} 1 & 0 \\ 0 & e^{-(\alpha+\beta)t} \end{bmatrix}\begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ 1 & -1 \end{bmatrix}, \\
&= \begin{bmatrix} 1 & \frac{\alpha}{\alpha+\beta} \\ 1 & -\frac{\beta}{\alpha+\beta} \end{bmatrix}\begin{bmatrix} \frac{\beta}{\alpha+\beta} & \frac{\alpha}{\alpha+\beta} \\ e^{-(\alpha+\beta)t} & -e^{-(\alpha+\beta)t} \end{bmatrix}, \\
&= \begin{bmatrix} \frac{\beta}{\alpha+\beta} + \frac{\alpha}{\alpha+\beta}e^{-(\alpha+\beta)t} & \frac{\alpha}{\alpha+\beta} - \frac{\alpha}{\alpha+\beta}e^{-(\alpha+\beta)t} \\ \frac{\beta}{\alpha+\beta} - \frac{\beta}{\alpha+\beta}e^{-(\alpha+\beta)t} & \frac{\alpha}{\alpha+\beta} + \frac{\beta}{\alpha+\beta}e^{-(\alpha+\beta)t} \end{bmatrix}.
\end{aligned}$$

This is the general solution of the two-state process, and from equation (7.31) we deduce that:

$$\mathbf{P}(t) = \begin{bmatrix} \frac{\beta}{\alpha+\beta} + \frac{\alpha}{\alpha+\beta}e^{-(\alpha+\beta)t} & \frac{\alpha}{\alpha+\beta} - \frac{\alpha}{\alpha+\beta}e^{-(\alpha+\beta)t} \\ \frac{\beta}{\alpha+\beta} - \frac{\beta}{\alpha+\beta}e^{-(\alpha+\beta)t} & \frac{\alpha}{\alpha+\beta} + \frac{\beta}{\alpha+\beta}e^{-(\alpha+\beta)t} \end{bmatrix}.$$

This simple case is mentioned in the Wikipedia website (Wikipedia, 2014). Recall that:

$$n_j(t) = \sum_{k=1}^{p} n_k(0)P_{kj}(t),$$

so therefore

$$\begin{aligned}\lim_{t\to\infty} n_j(t) &= \sum_{k=1}^{p} \lim_{t\to\infty} n_k(0)P_{kj}(t), \\ &= \lim_{t\to\infty} n_1(0)P_{1j}(t) + \lim_{t\to\infty} n_2(0)P_{2j}(t) + \cdots + \lim_{t\to\infty} n_p(0)P_{pj}(t).\end{aligned}$$

In the 2×2 case and for $j = 1$:

$$\begin{aligned}\lim_{t\to\infty} n_1(t) &= \lim_{t\to\infty} n_1(0)P_{11}(t) + \lim_{t\to\infty} n_2(0)P_{21}(t), \\ &= \frac{\beta}{\alpha+\beta} n_1(0) + \frac{\beta}{\alpha+\beta} n_2(0), \\ &= \frac{\beta n}{\alpha+\beta}.\end{aligned}$$

Similarly for $j = 2$:

$$\lim_{t\to\infty} n_2(t) = \frac{\alpha n}{\alpha+\beta}.$$

This implies that when time becomes large then our system approaches a unique equilibrium solution.

(ii) The $p \times p$ Case:

Next, we investigate the existence and uniqueness of the equilibrium when time goes to infinity in the case that the matrix $\mathbf{Q}$ is of size $p \times p$. We follow the same approach and construct a matrix $\mathbf{E}$ with rows consisting of p independent eigenvectors

e of the matrix **Q**:

$$\mathbf{E} = \begin{pmatrix} e_{11} & e_{12} & \dots & e_{1p} \\ e_{21} & e_{22} & \dots & e_{2p} \\ \vdots & & \ddots & \vdots \\ e_{p1} & e_{p2} & \dots & e_{pp} \end{pmatrix}.$$

The eigenvector $(e_{11}, e_{12}, \dots, e_{1p})$ corresponds to the eigenvalue $\lambda = 0$, with $\sum_{i=1}^{p} e_{1i} = 1$, and $e_{1i} > 0$ for $i = 1, 2, \dots p$. Suppose that the inverse of the matrix **E** is:

$$\mathbf{E}^{-1} = \begin{pmatrix} f_{11} & f_{12} & \dots & f_{1p} \\ f_{21} & f_{22} & \dots & f_{2p} \\ \vdots & & \ddots & \vdots \\ f_{p1} & f_{p2} & \dots & f_{pp} \end{pmatrix}.$$

The Jordan normal form of the $p \times p$ matrix $\boldsymbol{Q}$ is given by the block diagonal matrix **J**:

$$\mathbf{J} = \mathbf{E}\mathbf{Q}\mathbf{E}^{-1} = \left[\begin{array}{c|ccc} 0 & \dots & \dots & 0 \\ \hline \vdots & \ddots & & \vdots \\ 0 & & \ddots & \end{array}\right].$$

Hence:

$$\mathbf{J} = \begin{bmatrix} 0 & 0 & 0 & \dots & 0 \\ 0 & \mathbf{J}_1 & & \dots & 0 \\ 0 & 0 & \mathbf{J}_2 & \dots & 0 \\ \vdots & \vdots & & \ddots & \vdots \\ 0 & 0 & \dots & \dots & \mathbf{J}_k \end{bmatrix},$$

where $\mathbf{J}_1, \mathbf{J}_2, \dots \mathbf{J}_k$ are square matrices of size $p \times p$, with the eigenvalues λ on the

diagonal and 1 on the diagonal above and zero everywhere else:

$$\mathbf{J}_l = \begin{bmatrix} \lambda & 1 & \dots & \dots \\ 0 & \lambda & 1 & \dots \\ \vdots & \vdots & \ddots & 1 \\ 0 & \dots & \dots & \lambda \end{bmatrix},$$

where $l = 1, 2, \dots k$ and the real parts of the eigenvalues are non-positive such that $\mathfrak{Re}(\lambda) < 0$. Now we shall present the following lemma to complete the proof of Theorem 7.3.2.

Lemma 7.3.3. *We assert that*

$$e^{\mathbf{J}_l t} = \begin{bmatrix} e^{\lambda t} & & \dots & \\ 0 & e^{\lambda t} & \dots & \\ \vdots & \vdots & \ddots & \vdots \\ 0 & \dots & \dots & e^{\lambda t} \end{bmatrix},$$

with entries above the diagonal powers of t multiplied by $e^{\lambda t}$, and those under the diagonal are zero.

Proof. Let consider the power of matrix $(\mathbf{J}_l)^i$ with positive integer powers i where $i = 1, 2, \dots k$. Thus, for $i = 1$ we deduce that:

$$\mathbf{J}_l = \begin{bmatrix} \lambda & 1 & \dots & \dots \\ 0 & \lambda & 1 & \dots \\ \vdots & \vdots & \ddots & 1 \\ 0 & \dots & \dots & \lambda \end{bmatrix},$$

and for $i = 2$:

$$\mathbf{J}_l^2 = \begin{bmatrix} \lambda^2 & 2\lambda & 1 & \dots & 0 \\ 0 & \lambda^2 & 2\lambda & 1 & \vdots \\ \vdots & \vdots & & \ddots & 2\lambda \\ 0 & \dots & & \dots & \lambda^2 \end{bmatrix}.$$

Similarly for $i = 3$:

$$\mathbf{J}_l^3 = \begin{bmatrix} \lambda^3 & 3\lambda^2 & 3\lambda & 1 & \dots & 0 \\ 0 & \lambda^3 & 3\lambda^2 & 3\lambda & 1 & \vdots \\ \vdots & \vdots & & \ddots & \vdots & 3\lambda^2 \\ 0 & \dots & & \dots & \dots & \lambda^3 \end{bmatrix}.$$

Finally when $i = k$, we deduce that:

$$\mathbf{J}_l^k = \begin{bmatrix} \lambda^k & \binom{k}{1}\lambda^{k-1} & \binom{k}{2}\lambda^{k-2} & \dots & 1 & 0 & \dots & 0 \\ 0 & \lambda^k & \binom{k}{1}\lambda^{k-1} & \binom{k}{2}\lambda^{k-2} & \dots & \vdots & & \vdots \\ \vdots & \vdots & \vdots & & \ddots & \vdots & \lambda^k & \binom{k}{1}\lambda^{k-1} \\ 0 & 0 & \dots & & \dots & \dots & 0 & \lambda^k \end{bmatrix}. \tag{7.41}$$

In this matrix we obtain that the main diagonal is λ^k, the one above it $\binom{k}{1}\lambda^{k-1}$. Moreover, the one above that is $\binom{k}{2}\lambda^{k-2}$, and so on until we either reach 1, $(k \leq p-1)$ or $\binom{k}{p-1}\lambda^{k-p+1}$ $(k \geq p-1)$.

We shall prove the expression of (7.41) by mathematical induction. The hypotheses of mathematical induction are satisfied for $k = 1, 2, 3$, and clearly we can see that the elements of the leading diagonal are all λ^k and the elements of the second

upper diagonal are of the form $\binom{k}{1}\lambda^{k-1}$. Let suppose that the result is true for $k-1$ and we want to prove that if is true for k. Consider the s^{th} upper diagonal where $s\geq 3$. By using the definition of matrix multiplication it is clear that:

$$\mathbf{J}_l^k = \mathbf{J}_l^{k-1}\ \mathbf{J}_l.$$

Hence:

$$\mathbf{J}_l^k = \left(\begin{array}{c|cccccccc} \lambda^{k-1} & \binom{k-1}{1}\lambda^{k-2} & \binom{k-1}{2}\lambda^{k-3} & \dots & 1 & 0 & \dots & 0 \\ 0 & \lambda^{k-1} & \binom{k-1}{1}\lambda^{k-2} & \binom{k-1}{2}\lambda^{k-3} & \ddots & & \vdots & \vdots \\ \vdots & \vdots & \vdots & & & \ddots & \vdots & \binom{k}{1}\lambda^{k-1} \\ 0 & \dots & \dots & & & \dots & \dots & \lambda^{k-1} \end{array}\right)$$

$$\times \left(\begin{array}{cccc|c|c} \lambda & 1 & \dots & \dots & 0 & \dots \\ 0 & \lambda & 1 & \dots & 0 & \dots \\ & & & \ddots & \vdots & \dots \\ \vdots & \vdots & \vdots & \lambda & 1 & \dots \\ \dots & \dots & \dots & \dots & \lambda & \dots \end{array}\right).$$

Now we shall find the element of the s^{th} upper diagonal $(\mathbf{J}_l^k)$, where $(1 \leq s \leq p-1)$.

$$\begin{aligned} &\text{If} \quad s > k+1, && (\mathbf{J}_l^k)_{1s} = 0. \\ &\text{If} \quad s = k+1, && (\mathbf{J}_l^k)_{1s} = 1 = \binom{k}{s-1}\lambda^{k-s+1}. \\ &\text{If} \quad s = k, && (\mathbf{J}_l^k)_{1s} = \binom{k-1}{k-2}\lambda^{k-(k-1)} + \lambda \times 1, \\ & && \quad = k\lambda = 1 \times \binom{k}{s-1}\lambda^{k-s+1}, \end{aligned}$$

$$
\begin{aligned}
\text{If} \quad s \;=\; k-1, \qquad\qquad (\mathbf{J}_l^k)_{1s} &= 1 \times \tbinom{k-1}{k-3}\lambda^{k-(k-2)} + \lambda\tbinom{k-1}{k-2}\lambda^{k-(k-1)}, \\
&= \lambda^2\big[\tbinom{k-1}{k-3} + \tbinom{k-1}{k-2}\big], \\
&= \lambda^2\left[\frac{1}{2}(k-1)(k-2) + (k-1)\right], \\
&= \frac{1}{2}k(k-1)\lambda^2, \\
&= \tbinom{k}{s-1}\lambda^{k-(k-2)}.
\end{aligned}
$$

Finally if $s = k - t$ and $2 \leq t \leq k-1$ we deduce that:

$$
\begin{aligned}
\tbinom{k-1}{k-t-2}\lambda^{k-(k-t-1)} + \lambda\tbinom{k-1}{k-t-1}\lambda^{k-(k-t)} &= \lambda^{t+1}\big[\tbinom{k-1}{k-t-2} + \tbinom{k-1}{k-t-1}\big], \\
&= \lambda^{t+1}\Big[\frac{(k-1)!}{(k-t-2)!(t+1)!} + \frac{(k-1)!}{(k-t-1)!t!}\Big], \\
&= \lambda^{t+1}\frac{(k-1)!}{(k-t-1)!(t+1)!}\big[k-t-1+t+1\big], \\
&= \lambda^{t+1}\frac{k!}{(k-t-1)!(t+1)!}, \\
&= \lambda^{t+1}\tbinom{k}{k-t-1}, \\
&= \tbinom{k}{s-1}\lambda^{k-s+1}.
\end{aligned}
$$

Thus we have shown that mathematical induction implies that the statement is true for all k. Hence in $\mathbf{J}_l^k$ the terms in the s^{th} upper diagonal are of the form:

$$
\tbinom{k}{s-1}\lambda^{k-s+1} \qquad\qquad \text{where} \quad 1 \leq s \leq k+1,
$$

and

$$
\text{zero} \qquad\qquad \text{where} \quad s > k+1.
$$

Thus we obtained that:

$$e^{\mathbf{J}_l t} = \sum_{k=0}^{\infty} \frac{(\mathbf{J}_l^k t)^k}{k!},$$

the entries in the lower diagonals are zero. The entries in the s^{th} upper diagonal are:

$$\begin{aligned}
\sum_{k=s-1}^{\infty} \frac{t^k}{k!} \binom{k}{s-1} \lambda^{k-s+1} &= \sum_{k=s-1}^{\infty} \frac{t^k}{(s-1)!(k-s+1)!} \lambda^{k-s+1}, \\
&= \sum_{m=0}^{\infty} \frac{t^{m+s-1}}{(s-1)!m!} \lambda^m, \\
&= \frac{t^{s-1}}{(s-1)!} e^{\lambda t},
\end{aligned}$$

in other words we can see that a power of t multiplied by $e^{\lambda t}$ which proves Lemma 7.3.3. □

The second part, as we have,

$$e^{\mathbf{Q}t} = \mathbf{E}^{-1} e^{\mathbf{J}t}\ \mathbf{E},$$

then that as $t \to \infty$, $e^{\mathbf{Q}t}$ approaches:

$$\mathbf{E}^{-1} \left(\begin{array}{c|ccc} 1 & 0 & \dots & 0 \\ \hline 0 & \ddots & \dots & 0 \\ \vdots & & \ddots & 0 \\ 0 & & \dots & 0 \end{array} \right) \mathbf{E}$$

$$= \begin{pmatrix} f_{11} & f_{12} & \dots & f_{1p} \\ \vdots & \ddots & & \vdots \\ \vdots & & \ddots & \vdots \\ f_{p1} & f_{p2} & \dots & f_{pp} \end{pmatrix} \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & \ddots & & \vdots \\ \vdots & & \ddots & \vdots \\ 0 & \dots & \dots & 0 \end{pmatrix} \begin{pmatrix} e_{11} & e_{12} & \dots & e_{1p} \\ \vdots & \ddots & & \vdots \\ \vdots & & \ddots & \vdots \\ e_{p1} & e_{p2} & \dots & e_{pp} \end{pmatrix},$$

$$= \begin{pmatrix} f_{11} & f_{12} & \dots & f_{1p} \\ \vdots & \ddots & & \vdots \\ \vdots & & \ddots & \vdots \\ f_{p1} & f_{p2} & \dots & f_{pp} \end{pmatrix} \begin{pmatrix} e_{11} & e_{12} & \dots & e_{1p} \\ 0 & \ddots & & 0 \\ \vdots & & \ddots & \vdots \\ 0 & 0 & \dots & 0 \end{pmatrix},$$

$$= \begin{pmatrix} f_{11}e_{11} & f_{11}e_{12} & \dots & f_{11}e_{1p} \\ f_{21}e_{11} & f_{21}e_{12} & \dots & f_{21}e_{1p} \\ \vdots & & \ddots & \vdots \\ f_{p1}e_{11} & f_{p1}e_{12} & \dots & f_{p1}e_{1p} \end{pmatrix}.$$

However, we have shown earlier that:

$$\mathbf{J} = \mathbf{EQE}^{-1},$$

hence we deduce the following:

$$\mathbf{QE}^{-1} \;=\; \mathbf{E}^{-1}\mathbf{J},$$

$$= \begin{pmatrix} f_{11} & f_{12} & \dots & f_{1p} \\ \vdots & \ddots & & \vdots \\ \vdots & & \ddots & \vdots \\ f_{p1} & f_{p2} & \dots & f_{pp} \end{pmatrix} \left(\begin{array}{c|ccc} 0 & 0 & \dots & 0 \\ \hline \vdots & \ddots & & \vdots \\ \vdots & & \text{not zero} & \vdots \\ 0 & \dots & \dots & \dots \end{array}\right),$$

$$= \left(\begin{array}{c|c} 0 & \dots \\ \hline \vdots & \text{not zero} \\ \hline 0 & \dots \end{array}\right).$$

Clearly we can see that the first column of the matrix $\mathbf{QE}^{-1}$ is zero, whilst the first column of the matrix $\mathbf{QE}^{-1}$ has i^{th} element, which can be expressed as:

$$\left(\begin{array}{c} i^{th} \text{ row of the matrix } \mathbf{Q} \end{array} \right) \begin{pmatrix} f_{11} \\ f_{21} \\ \vdots \\ f_{p1} \end{pmatrix} = 0.$$

This leads us to the fact that the vector $\begin{pmatrix} f_{11} \\ f_{21} \\ \vdots \\ f_{p1} \end{pmatrix}$ is a right eigenvector of the matrix $\mathbf{Q}$ with the eigenvalue $\lambda = 0$. Note that the corresponding eigenspace has dimension

one. Recall, that we find zero is a simple eigenvalue of $\mathbf{Q}$ and the eigenvector

$$\mathbf{1} = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix},$$

is another vector in it. Therefore:

$$\begin{pmatrix} f_{11} \\ f_{21} \\ \vdots \\ f_{p1} \end{pmatrix} = k \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix}, \qquad \text{for some constant } k.$$

From the definition of $\mathbf{E}\mathbf{E}^{-1} = \mathbf{I}$, we deduce that:

$$\begin{aligned} \begin{pmatrix} e_{11} & e_{12} & \dots & e_{1p} \end{pmatrix} \begin{pmatrix} f_{11} \\ f_{21} \\ \vdots \\ f_{p1} \end{pmatrix} &= 1, \\ &= k(e_{11} + e_{12} + \cdots + e_{1p}), \\ &= k, \end{aligned}$$

from our previous assumption $e_{11} + e_{12} + \cdots + e_{1p} = 1$. This leads to the following

results:

$$k = 1, \qquad \begin{pmatrix} f_{11} \\ f_{21} \\ \vdots \\ f_{p1} \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix},$$

and

$$\mathbf{E}^{-1} \left(\begin{array}{c|c} 1 & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{0} \end{array} \right) \mathbf{E} = \begin{pmatrix} e_{11} & e_{12} & \dots & e_{1p} \\ e_{11} & e_{12} & \dots & e_{1p} \\ \vdots & & \ddots & \vdots \\ e_{11} & e_{12} & \dots & e_{1p} \end{pmatrix},$$

consequently we prove that $P_{ik} \to e_{1k}$ as time goes to infinity. In conclusion, we deduce that:

$$n_k(t) = n_1(0)P_{1k}(t) + n_2(0)P_{2k}(t) + \cdots + n_p(0)P_{pk}(t),$$

as $t \to \infty$:

$$(n_1(0) + n_2(0) + \cdots + n_p(0))e_{1k} = ne_{1k}.$$

This completes our proof by showing that our system approaches the unique equilibrium distribution as time becomes large. □

The next section shall discuss the local and global stability of the extended model. We will show that when $R_0 \leq 1$ our model has only the disease-free equilibrium which is globally asymptotically stable, this implies that HCV dies out eventually in addicts groups and shooting galleries.

7.4 Stability Analysis

The stability of the equilibrium solutions is important in the study of mathematical models. In this section, we present the results of stability analysis of the equilibrium points. The extended model has two non-negative equilibrium points namely:

- The disease-free equilibrium.
- The endemic equilibrium.

In the next theorem we will show that the disease-free equilibrium solution is the only solution if $R_0 \leq 1$. Moreover, we prove that under the condition that $R_0 \leq 1$ the disease-free equilibrium is globally asymptotically stable, which means that eventually the disease will die out.

Theorem 7.4.1. *Suppose that for each pair of groups i and k of addicts there exists a shooting gallery j_0 with $P_{ij_0}(1-\phi_{ij_0})\Lambda_{kj_0} > 0$. Then, if $R_0 \leq 1$ the model system (7.12)-(7.20) has a unique disease-free equilibrium which is globally asymptotically stable.*

Proof. To prove this theorem, we aim to prove several results that give upper bounds on the limit supremum of each group i of addicts and shooting gallery j in terms of $\pi^{\infty}_{h_1 i}$ or $\pi^{\infty}_{h_2 i}$. From equation (7.14) and equation (7.15) we can express the link between $\pi^{\infty}_{h_1 i}$ and $\pi^{\infty}_{h_2 i}$. We write $\pi^{\infty}_{h_1 i}$ for $\limsup_{t\to\infty} \pi_{h_1 i}(t)$. Similarly, we define:

$$\begin{aligned}
\pi^{\infty}_{h_2 i} &= \limsup_{t\to\infty} \pi_{h_2 i}(t), \\
\pi^{\infty}_{y i} &= \limsup_{t\to\infty} \pi_{y i}(t), \\
\pi^{\infty}_{z i} &= \limsup_{t\to\infty} \pi_{z i}(t).
\end{aligned}$$

Again for the needle system, we have:

$$\begin{aligned}\beta^{\infty}_{h_1 j} &= \limsup_{t\to\infty} \beta_{h_1 j}(t),\\ \beta^{\infty}_{h_2 j} &= \limsup_{t\to\infty} \beta_{h_2 j}(t),\\ \beta^{\infty}_{yj} &= \limsup_{t\to\infty} \beta_{yj}(t).\end{aligned}$$

This theorem needs some preliminary results to prove first.

Lemma 7.4.2.

$$\pi^{\infty}_{yi} \leq \frac{\sigma\pi^{\infty}_{h_1 i} + \sum_{\substack{k=1\\k\neq i}}^{p} \omega_{ki}\frac{n^*_k}{n^*_i}\pi^{\infty}_{yk}}{\mu + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}.$$

Proof. We use a similar technique as in the proof of Lemma 3.1.5 with equation (7.16), the fact that $n_i \longrightarrow n^*_i$ and $n_k \longrightarrow n^*_k$ as $t \longrightarrow \infty$ and the equilibrium group size equations. □

Using a similar argument it is straightforward to show:

$$\pi^{\infty}_{zi} \leq \frac{\alpha\sigma\pi^{\infty}_{h_2 i} + \sum_{\substack{k=1\\k\neq i}}^{p} \omega_{ki}\frac{n^*_k}{n^*_i}\pi^{\infty}_{zk}}{\mu + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}, \tag{7.42}$$

$$\beta^{\infty}_{h_1 j} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_1 i}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}, \tag{7.43}$$

$$\beta^{\infty}_{h_2 j} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_2 i}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}, \tag{7.44}$$

$$\beta^{\infty}_{yj} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{yi}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}. \tag{7.45}$$

The next lemma will state the relationship between $\pi^{\infty}_{h_1 i}$ and $\pi^{\infty}_{h_2 i}$ by using equations (7.14) and (7.15).

Lemma 7.4.3.

$$\frac{\pi^{\infty}_{h_1 i}}{1-\delta} = \frac{\pi^{\infty}_{h_2 i}}{\delta}.$$

Proof. Let $\xi_i = \frac{\pi_{h_1 i}}{1-\delta} - \frac{\pi_{h_2 i}}{\delta}$. Subtracting equation (7.15) divided by $1-\delta$ from equation (7.14) divided by δ gives:

$$\frac{d\xi_i}{dt} = -(\mu+\sigma)\xi_i + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ki}\xi_k \frac{n_k}{n_i} - \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ki}\xi_i \frac{n_k}{n_i}.$$

Denote $\xi_k^{\infty} = \limsup_{t\to\infty} \xi_k(t)$, and assume that $\sup_{k=1,2,\ldots p} \xi_k^{\infty} > 0$, and let $\xi_{k_0}^{\infty} = \sup_{k=1,2,\ldots p} \xi_k^{\infty}$. If we have $\xi_{k_0}^{\infty} > 0$ then for a given $\epsilon > 0$ there exists t_0 such that for $t \geq t_0$:

$$\frac{d\xi_{k_0}}{dt} \leq -(\mu+\sigma)\xi_{k_0} + \sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{kk_0}\xi_k^{\infty} \frac{n_k^*}{n_{k_0}^*} - \sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{kk_0}\xi_{k_0} \frac{n_k^*}{n_{k_0}^*} + \epsilon.$$

Using the equilibrium solution of the system (7.1) gives:

$$\sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{kk_0} \frac{n_k^*}{n_{k_0}^*} = \sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{k_0 k}.$$

Thus:

$$\frac{d\xi_{k_0}}{dt} \leq -(\mu+\sigma)\xi_{k_0} + \sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{kk_0}\xi_k^{\infty} \frac{n_k^*}{n_{k_0}^*} - \sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{k_0 k}\xi_{k_0} + \epsilon.$$

Thus for $t \geq t_0(\epsilon)$ we deduce that:

$$\frac{d}{dt}\left(\xi_{k_0} \exp\left[\mu+\sigma+\sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{k_0 k}\right] t\right) \leq \left(\sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{kk_0}\xi_k^{\infty} \frac{n_k^*}{n_{k_0}^*} + \epsilon\right) \exp\left[\left(\mu+\sigma+\sum_{\substack{k=1 \\ k\neq k_0}}^{p} \omega_{k_0 k}\right) t\right].$$

Integrating over $[t_0(\epsilon), t)$ gives:

$$\begin{aligned}\xi_{k_0} \exp\left(\left[\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}\right]t\right) &\leq \xi_{k_0}(t_0(\epsilon)) \\ &+ \frac{\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{kk_0}\xi_k^{\infty}\frac{n_k^*}{n_{k_0}^*}+\epsilon}{\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}}\left[\exp\left(\left[\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}\right]t\right)\right. \\ &- \left.\exp\left(\left[\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}\right]t_0(\epsilon)\right)\right].\end{aligned}$$

Dividing by $\exp\left[\left(\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}\right)t\right]$ and taking the limsup and letting $t\longrightarrow\infty$,

$$\xi_{k_0}^{\infty} \leq \frac{\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{kk_0}\xi_k^{\infty}\frac{n_k^*}{n_{k_0}^*}+\epsilon}{\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}}.$$

Letting $\epsilon\longrightarrow 0$ gives:

$$\xi_{k_0}^{\infty} \leq \frac{\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{kk_0}\xi_{k_0}^{\infty}\frac{n_k^*}{n_{k_0}^*}}{\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}}.$$

Dividing both sides by $\xi_{k_0}^{\infty}$ gives:

$$1 \leq \frac{\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}}{\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{k_0k}} < 1. \tag{7.46}$$

Thus we have a contradiction in (7.46) which implies that $\xi_{k_0}^{\infty} \leq 0$. Hence $\xi_k^{\infty} \leq 0$ for $k = 1, 2, \ldots p$. Similarly, let $\eta_i = \frac{\pi_{h_2 i}}{\delta} - \frac{\pi_{h_1 i}}{1-\delta} = -\xi_i$, and denote $\eta_k^{\infty} = \limsup_{t\longrightarrow\infty}\eta_k(t)$

and $\eta_{k,\infty} = \liminf_{t\longrightarrow\infty} \eta_k(t)$ and $\xi_{k,\infty} = \liminf_{t\longrightarrow\infty} \xi_k(t)$:

$$\eta_k^\infty = -(-\eta_{k,\infty}) = -(\xi_{k,\infty}) \leq 0 \qquad \text{for} \quad k = 1, 2, \ldots p.$$

By using a similar argument we can show that $\eta_k^\infty \leq 0$ for $k = 1, 2, \ldots p$. Thus:

$$\xi_{k,\infty} \geq 0.$$

Hence:

$$\begin{aligned} 0 &\geq \xi_k^\infty \geq \xi_{k,\infty} \geq 0. \\ \xi_k^\infty &= \xi_{k,\infty} = 0. \end{aligned}$$

Thus $\xi_k \longrightarrow 0$ as $t \longrightarrow \infty$, for each $k = 1, 2, \ldots p$. Lemma 7.4.3 follows.

□

Recall that we are proving the global stability of the disease-free steady state under the condition $R_0 \leq 1$. Let $\pi_{hi} = \pi_{h_1 i} + \pi_{h_2 i}$. It is sufficient to prove that $\pi_{hi}^\infty = 0$. In order to do this suppose that $\pi_{h_1 i}^\infty > 0$. From the proof of Lemma 7.4.3, it is straightforward to prove:

$$\pi_{hi}^\infty = \frac{\pi_{h_1 i}^\infty}{1-\delta} = \frac{\pi_{h_2 i}^\infty}{\delta}. \tag{7.47}$$

By Lemma 7.4.2:

$$\pi_{yi}^\infty \leq \frac{\sigma(1-\delta)\pi_{hi}^\infty + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ki} \frac{n_k^*}{n_i^*} \pi_{yk}^\infty}{\mu + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ik}}. \tag{7.48}$$

Adding equations (7.14) and (7.15) together and using the inequalities (7.43) - (7.45),

the fact that $n_i \longrightarrow n_i^*$ and $n_k \longrightarrow n_k^*$ as $t \longrightarrow \infty$ and the equilibrium group size equations we deduce that given $\epsilon > 0$ there exists t_0 such that for $t \geq t_0$

$$\begin{aligned}
\frac{d\pi_{hi}}{dt} &\leq (1-\pi_{hi}-\pi_{yi}-\pi_{zi})\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left[\frac{\alpha_h\sum_{k=1}^{p}\Lambda_{kj}\pi_{hk}^{\infty}+\alpha_y\sum_{k=1}^{p}\Lambda_{kj}\pi_{yk}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}\right] \\
&\quad -(\mu+\sigma)\pi_{hi}+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n_k^*}{n_i^*}\pi_{hk}^{\infty}-\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}\pi_{hi}+\epsilon, \\
&\leq (1-\pi_{hi})\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left[\frac{\alpha_h\sum_{k=1}^{p}\Lambda_{kj}\pi_{hk}^{\infty}+\alpha_y\sum_{k=1}^{p}\Lambda_{kj}\pi_{yk}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}\right] \\
&\quad -(\mu+\sigma)\pi_{hi}+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n_k^*}{n_i^*}\pi_{hk}^{\infty}-\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}\pi_{hi}+\epsilon.
\end{aligned}$$

Arguing as earlier, it is easy to show that:

$$\pi_{hi}^{\infty} \leq \frac{\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\alpha_h\sum_{k=1}^{p}\Lambda_{kj}\pi_{hk}^{\infty}+\alpha_y\sum_{k=1}^{p}\Lambda_{kj}\pi_{yk}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}\right)+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n_k^*}{n_i^*}\pi_{hk}^{\infty}}{\mu+\sigma+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}+\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\alpha_h\sum_{k=1}^{p}\Lambda_{kj}\pi_{hk}^{\infty}+\alpha_y\sum_{k=1}^{p}\Lambda_{kj}\pi_{yk}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}\right)}.$$

Now we want to obtain an upper bound for π_{hi}^{∞} in terms of π_{hk}^{∞} only. Thus, we ignore the last term in the sum in the denominator and reapply the inequality (7.48) many times to replace π_{yk}^{∞} with terms involving sums of π_{hk}^{∞}:

$$\begin{aligned}
&\leq \frac{1}{\mu+\sigma+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}\left[\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\alpha_h\sum_{k=1}^{p}\Lambda_{kj}\pi_{hk}^{\infty}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}\right.\right. \\
&+ \frac{\sigma(1-\delta)\alpha_y\sum_{k=1}^{p}\Lambda_{kj}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}\left(\frac{\pi_{hk}^{\infty}}{\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}}+\frac{\sum_{\substack{l_2=1\\l_2\neq k}}^{p}\omega_{l_2k}\frac{n_{l_2}^*}{n_k^*}\pi_{hl_2}^{\infty}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}\right)\left(\mu+\sum_{\substack{k_2=1\\k_2\neq l_2}}^{p}\omega_{l_2k_2}\right)}\right.
\end{aligned}$$

$$+ \quad \frac{\sum_{\substack{l_2=1\\l_2\neq k}}^{p}\sum_{\substack{l_3=1\\l_3\neq l_2}}^{p}\omega_{l_3l_2}\omega_{l_2k}\frac{n^*_{l_3}}{n^*_k}\pi^{\infty}_{hl_3}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}\right)\left(\mu+\sum_{\substack{k_2=1\\k_2\neq l_2}}^{p}\omega_{l_2k_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l_3}}^{p}\omega_{l_3k_3}\right)}+\ldots\Bigg)\Bigg)$$

$$+ \quad \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n^*_k}{n^*_i}\pi^{\infty}_{hk}\Bigg],$$

$$\pi^{\infty}_{hi} \quad \leq \quad \sum_{k=1}^{p}Q^*_{ik}\pi^{\infty}_{hk}, \tag{7.49}$$

where

$$Q^*_{ik} = \frac{1}{\mu+\sigma+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}\Bigg[\sum_{j=1}^{q}\lambda_iP_{ij}(1-\phi_{ij})\Bigg(\frac{\alpha_h\Lambda_{kj}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}$$

$$+ \quad \frac{\sigma(1-\delta)\alpha_y}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j}\Bigg[\frac{\Lambda_{kj}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}\right)}+\frac{\sum_{\substack{l_2=1\\l_2\neq k}}^{p}\Lambda_{l_2j}\omega_{kl_2}\frac{n^*_k}{n^*_{l_2}}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}\right)\left(\mu+\sum_{\substack{k_2=1\\k_2\neq k}}^{p}\omega_{kk_2}\right)}$$

$$+ \quad \frac{\sum_{\substack{l_2=1\\l_2\neq k}}^{p}\sum_{\substack{l_3=1\\l_3\neq l_2}}^{p}\Lambda_{l_3j}\ \omega_{kl_2}\omega_{l_2l_3}\frac{n^*_k}{n^*_{l_3}}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}\right)\left(\mu+\sum_{\substack{k_2=1\\k_2\neq k}}^{p}\omega_{kk_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l_2}}^{p}\omega_{l_2k_3}\right)}+\ldots\Bigg]\Bigg)$$

$$+ \quad I(k\neq i)\omega_{ki}\frac{n^*_k}{n^*_i}\Bigg]. \tag{7.50}$$

It is clear that the disease-free equilibrium $\pi^*_{x_1i}=1$ and $\pi^*_{x_1i}=\pi^*_{h_1i}=\pi^*_{h_2i}=\pi^*_{yi}=\pi^*_{zi}=0$, also $\beta^*_{h_1j}=\beta^*_{h_2j}=\beta^*_{yj}=0$ is always a solution to the differential equations system (7.12) – (7.20). We need to show that if $R_0\leq 1$ then there is no other equilibrium solution. To show that we need the following lemma:

Lemma 7.4.4. *The matrix* $\mathbf{Q}^*$ *is defined in the formula (7.50) and the matrix* $\mathbf{Q}^T$*, where* $\mathbf{Q}^T$ *is the transpose of the matrix* Q_{ik} *defined in the formula (7.27) satisfy*

$$Q_{ik}^T = Q_{ki},$$

so they have the same eigenvalues and spectral radius.

Proof. Using a similar argument as in the proof of Lemma 3.1.2 in our basic model we deduce:

$$Q_{ik}^T = Q_{ik}^* \frac{\left(\mu + \sigma + \sum_{\substack{k_1=1 \\ k_1 \neq i}}^{p} \omega_{ik_1}\right) n_i^*}{\left(\mu + \sigma + \sum_{\substack{k_1=1 \\ k_1 \neq k}}^{p} \omega_{kk_1}\right) n_k^*}. \tag{7.51}$$

The result is obtained, similarly to the proof of Lemma 3.1.2. □

To complete the proof of the global asymptotic stability (hence uniqueness) of the disease-free equilibrium if $R_0 \leq 1$, we recall that for each pair of groups i and k of addicts there exists a shooting gallery j_0 with:

$$P_{ij_0}(1 - \phi_{ij_0})\Lambda_{kj_0} > 0,$$

this means that transmission of the disease to each group of addicts is possible.

Let $R_0 \leq 1$ and suppose that $\pi_{hk^0} = \sup_{k=1,2,\ldots p} \pi_{hk}^{\infty} > 0$. A straightforward examination of the derivation of equation (7.49) shows that in fact:

$$\pi_{hi}^{\infty} \leq \frac{\sum_{k=1}^{p} Q_{ik}^* \pi_{hk}^{\infty}}{1 + \sum_{k=1}^{p} R_{ik}^* \pi_{hk}^{\infty}}.$$

Here

$$R^*_{ik} = \frac{1}{\mu+\sigma+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}\sum_{j=1}^{q}\frac{\lambda_i P_{ij}(1-\phi_{ij})\alpha_h\Lambda_{kj}}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j},$$

so $\sum_{k=1}^{p} R^*_{ik}\pi^\infty_{hk} > 0$, thus:

$$\pi^\infty_{hi} < \sum_{k=1}^{p} Q^*_{ik}\pi^\infty_{hk}, \qquad \text{for} \quad i = 1, 2, \ldots p, \tag{7.52}$$

so there exists an ϵ_2 such that:

$$\boldsymbol{\pi}^\infty_h(1+\epsilon_2) < \boldsymbol{Q}^*\boldsymbol{\pi}^\infty_h,$$

where $\boldsymbol{\pi}^\infty_h = (\pi^\infty_{h1}, \pi^\infty_{h2}, \ldots, \pi^\infty_{hp}) \neq \mathbf{0}$. Arguing as at the end of the proof of Theorem 3.1.4 we deduce a contradiction and that $\pi^\infty_{hi} = 0$ for $i = 1, 2, \ldots p$. Hence from the inequality (7.48) each $\pi^\infty_{yi} = 0$ (otherwise we obtain a contradiction similarly to (7.46)). Similarly each $\pi^\infty_{zi} = 0$. Also from (7.43) - (7.45) we obtain that $\beta^\infty_{h_1 j} = \beta^\infty_{h_2 j} = \beta^\infty_{yj} = 0$. This completes the proof of Theorem 7.4.1 □

Now we are interested to predict the behaviour of the extended model when R_0 exceeds unity. In next theorem we shall prove the existence of the non-zero endemic equilibrium solution if $R_0 > 1$. However, before we start our discussion we need to present an important result about π^*_{hi}, $\pi^*_{h_1 i}$ and $\pi^*_{h_2 i}$.

Lemma 7.4.5. *For any equilibrium values of (7.12) – (7.20) and for $i = 1, 2, \ldots p$:*

$$\pi^*_{hi} = \frac{\pi^*_{h_1 i}}{1-\delta} = \frac{\pi^*_{h_2 i}}{\delta}.$$

Proof. Suppose that:

$$\frac{\pi^*_{h_1k_0}}{1-\delta} - \frac{\pi^*_{h_2k_0}}{\delta} = \sup_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_1i}}{1-\delta} - \frac{\pi^*_{h_2i}}{\delta}\right) > 0.$$

Then by dividing the equilibrium version of equation (7.14) with $i = k_0$ by $1-\delta$ and the equilibrium version of equation (7.15) with $i = k_0$ by δ and subtracting we deduce that:

$$\begin{aligned}\left(\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{kk_0}\frac{n^*_k}{n^*_{k_0}}\right)\left(\frac{\pi^*_{h_1k_0}}{1-\delta} - \frac{\pi^*_{h_2k_0}}{\delta}\right) &= \sum_{\substack{k=1\\k\neq k_0}}^{p}\left(\frac{\pi^*_{h_1k}}{1-\delta} - \frac{\pi^*_{h_2k}}{\delta}\right)\omega_{kk_0}\frac{n^*_k}{n^*_{k_0}},\\ &\leq \left(\frac{\pi^*_{h_1k_0}}{1-\delta} - \frac{\pi^*_{h_2k_0}}{\delta}\right)\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{kk_0}\frac{n^*_k}{n^*_{k_0}}.\end{aligned}$$

Hence

$$\mu+\sigma+\sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{kk_0}\frac{n^*_k}{n^*_{k_0}} \leq \sum_{\substack{k=1\\k\neq k_0}}^{p}\omega_{kk_0}\frac{n^*_k}{n^*_{k_0}},$$

which is a contradiction, so:

$$\sup_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_1i}}{1-\delta} - \frac{\pi^*_{h_2i}}{\delta}\right) \leq 0.$$

Similarly

$$0 \geq \sup_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_2i}}{\delta} - \frac{\pi^*_{h_1i}}{1-\delta}\right) = -\inf_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_1i}}{1-\delta} - \frac{\pi^*_{h_2i}}{\delta}\right).$$

Thus

$$0 \geq \sup_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_1i}}{1-\delta} - \frac{\pi^*_{h_2i}}{\delta}\right) \geq \inf_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_1i}}{1-\delta} - \frac{\pi^*_{h_2i}}{\delta}\right) \geq 0,$$

so

$$\sup_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_1 i}}{1-\delta}-\frac{\pi^*_{h_2 i}}{\delta}\right)=\inf_{i=1,2,\ldots p}\left(\frac{\pi^*_{h_1 i}}{1-\delta}-\frac{\pi^*_{h_2 i}}{\delta}\right)=0,$$

and

$$\frac{\pi^*_{h_1 i}}{1-\delta}=\frac{\pi^*_{h_2 i}}{\delta} \qquad \text{for } \; i=1,2,\ldots p.$$

As $\pi^*_{hi}=\pi^*_{h_1 i}+\pi^*_{h_2 i}$ the results of Lemma 7.4.5 holds. □

Theorem 7.4.6. *If $R_0>1$, there is a non-zero endemic equilibrium solution to the system (7.12) - (7.20).*

Proof. The proof is similar to the proof of Theorem 3.1.8. We begin our proof by finding the equilibrium point of π^*_{yi} expressed in terms of π^*_{hi} as follows:

$$\pi^*_{yi} \;=\; \frac{\sigma\pi^*_{h_1 i}}{\mu+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n^*_k}{n^*_i}}+\frac{\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n^*_k}{n^*_i}\pi^*_{yk}}{\mu+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n^*_k}{n^*_i}}. \tag{7.53}$$

From Lemma 7.4.5 and successively reapplying the equation (7.53) we can write the above as:

$$\begin{aligned}
\pi^*_{yi} \;=\;& \frac{\sigma(1-\delta)\pi^*_{hi}}{\mu+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}+\frac{\sum_{\substack{k=1\\k\neq i}}^{p}\sigma(1-\delta)\omega_{ki}\frac{n^*_k}{n^*_i}\pi^*_{hk}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{l=1\\l\neq k}}^{p}\omega_{kl}\right)}\\
&+\frac{\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\sum_{\substack{l=1\\l\neq k_1}}^{p}\sigma(1-\delta)\omega_{k_1 i}\omega_{lk_1}\frac{n^*_l}{n^*_i}\pi^*_{hl}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{k_2=1\\k_2\neq k_1}}^{p}\omega_{k_1 k_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l}}^{p}\omega_{lk_3}\right)}\\
&+\frac{\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\sum_{\substack{l=1\\l\neq k_1}}^{p}\sum_{\substack{k_2=1\\k_2\neq l}}^{p}\sigma(1-\delta)\omega_{k_1 i}\omega_{lk_1}\omega_{k_2 l}\frac{n^*_{k_2}}{n^*_i}\pi^*_{hk_2}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{\bar{k}_2=1\\\bar{k}_2\neq k_1}}^{p}\omega_{k_1\bar{k}_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l}}^{p}\omega_{lk_3}\right)\left(\mu+\sum_{\substack{k_4=1\\k_4\neq k_2}}^{p}\omega_{k_2 k_4}\right)}\\
&+\ldots\ .
\end{aligned} \tag{7.54}$$

Lastly re-labeling the dummy suffices so that the suffix of π_h in all terms except the first is k we obtain the following:

$$\begin{aligned}
\pi^*_{yi} &= \frac{\sigma(1-\delta)\pi^*_{hi}}{\mu+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}} + \frac{\sum_{\substack{k=1\\k\neq i}}^{p}\sigma(1-\delta)\omega_{ki}\frac{n^*_k}{n^*_i}\pi^*_{hk}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{l=1\\l\neq k}}^{p}\omega_{kl}\right)} \\
&+\frac{\sum_{k=1}^{p}\sum_{\substack{k_1=1\\k_1\neq k,i}}^{p}\sigma(1-\delta)\omega_{k_1i}\omega_{kk_1}\frac{n^*_k}{n^*_i}\pi^*_{hk}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{k_2=1\\k_2\neq k_1}}^{p}\omega_{k_1k_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq k}}^{p}\omega_{kk_3}\right)} \\
&+\frac{\sum_{k=1}^{p}\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\sum_{\substack{l=1\\l\neq k_1,k_2}}^{p}\sigma(1-\delta)\omega_{k_1i}\omega_{lk_1}\omega_{kl}\frac{n^*_k}{n^*_i}\pi^*_{hk}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{\overline{k}_2=1\\\overline{k}_2\neq k_1}}^{p}\omega_{k_1\overline{k}_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l}}^{p}\omega_{lk_3}\right)\left(\mu+\sum_{\substack{k_4=1\\k_4\neq k}}^{p}\omega_{kk_4}\right)} \\
&+\ldots\ . \qquad (7.55)
\end{aligned}$$

Equation (7.55) can be expressed in a matrix format as:

$$\boldsymbol{\pi}^*_y = \sigma(1-\delta)\mathbf{A}\boldsymbol{\pi}^*_h, \qquad (7.56)$$

where

$$\begin{aligned}
A_{ik} &= \frac{I(i=k)}{\mu+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n^*_k}{n^*_i}} + \frac{\omega_{ki}\frac{n^*_k}{n^*_i}I(i\neq k)}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{l=1\\l\neq k}}^{p}\omega_{kl}\right)} \\
&+\frac{\sum_{\substack{k_1=1\\k_1\neq k,i}}^{p}\omega_{k_1i}\omega_{kk_1}\frac{n^*_k}{n^*_i}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{k_2=1\\k_2\neq k_1}}^{p}\omega_{k_1k_2}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq k}}^{p}\omega_{kk_3}\right)} \\
&+\frac{\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\sum_{\substack{l=1\\l\neq k_1,k_2}}^{p}\omega_{k_1i}\omega_{lk_1}\omega_{kl}\frac{n^*_k}{n^*_i}}{\left(\mu+\sum_{\substack{k_1=1\\k_1\neq i}}^{p}\omega_{ik_1}\right)\left(\mu+\sum_{\substack{\overline{k_2}=1\\\overline{k_2}\neq k_1}}^{p}\omega_{k_1\overline{k_2}}\right)\left(\mu+\sum_{\substack{k_3=1\\k_3\neq l}}^{p}\omega_{lk_3}\right)\left(\mu+\sum_{\substack{k_4=1\\k_4\neq k}}^{p}\omega_{kk_4}\right)} \\
&+\ldots\ .
\end{aligned}$$

Similarly we obtain that:

$$\boldsymbol{\pi}_z^* = \sigma\alpha\delta\mathbf{A}\boldsymbol{\pi}_h^*. \tag{7.57}$$

Then we aim to find π_{hi}^* as a sum of $\pi_{h_1 i}^*$ and $\pi_{h_2 i}^*$:

$$\begin{aligned}
\pi_{hi}^* &= \pi_{h_1 i}^* + \pi_{h_2 i}^*, \\
&= \frac{1}{\mu + \sigma + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ik}} \Bigg[(1 - \pi_{hi}^* - \pi_{yi}^* - \pi_{zi}^*) \Bigg(\sum_{j=1}^{q} \lambda_i P_{ij} (1 - \phi_{ij}) \\
&\qquad (\alpha_h(\beta_{h_1 j}^* + \beta_{h_2 j}^*) + \alpha_y \beta_{yj}^*) \Bigg) + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ki} \frac{n_k^*}{n_i^*} \pi_{hk}^* \Bigg].
\end{aligned}$$

Substituting π_{yi}^* and π_{zi}^* by equations (7.56) and (7.57) and substituting for $\beta_{h_1 j}^*, \beta_{h_2 j}^*$ and β_{yj}^* gives:

$$\begin{aligned}
\pi_{hi}^* &= \frac{1}{\mu + \sigma + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ik}} \Bigg(\Bigg[1 - \Bigg(\sum_{k=1}^{p} \Big(\boldsymbol{I} + (\sigma(1-\delta) + \sigma\alpha\delta)\boldsymbol{A} \Big)_{ik} \pi_{hk}^* \Bigg) \Bigg] \\
&\qquad \sum_{j=1}^{q} \lambda_i P_{ij} (1 - \phi_{ij}) \frac{\sum_{k=1}^{p} \Lambda_{kj} (\alpha_h \pi_{hk}^* + \alpha_y \pi_{yk}^*)}{\sum_{k=1}^{p} \Lambda_{kj} + \tau_j} + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ki} \frac{n_k^*}{n_i^*} \pi_{hk}^* \Bigg),
\end{aligned}$$

where $\boldsymbol{I}$ denotes the identity matrix. Using equation (7.56) to substitute for π^*_{yk} we obtain:

$$\begin{aligned}
\pi^*_{hi} &= \frac{1}{\mu+\sigma+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}\Bigg(\Bigg[1-\Big[\Big(\boldsymbol{I}+(\sigma(1-\delta)+\sigma\alpha\delta)\boldsymbol{A}\Big)\boldsymbol{\pi}_h\Big]_i\Bigg] \\
&\quad \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\frac{\sum_{k=1}^{p}\Lambda_{kj}}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\Bigg[\alpha_h\pi^*_{hk}+\alpha_y\sigma(1-\delta)\Big(\boldsymbol{A}\boldsymbol{\pi}^*_h\Big)_k\Bigg] \\
&\quad + \sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n^*_k}{n^*_i}\pi^*_{hk}\Bigg), \\
&= \frac{1}{\mu+\sigma+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ik}}\Bigg(\Bigg[1-\Big[\Big(\boldsymbol{I}+(\sigma(1-\delta)+\sigma\alpha\delta)\boldsymbol{A}\Big)\boldsymbol{\pi}_h\Big]_i\Bigg] \\
&\quad \Bigg[\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\Bigg(\frac{\alpha_h\sum_{k=1}^{p}\Lambda_{kj}\pi^*_{hk}}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}+\frac{\alpha_y\sigma(1-\delta)}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\Bigg(\frac{\sum_{k=1}^{p}\Lambda_{kj}\pi^*_{hk}}{\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}} \\
&+ \frac{\sum_{\substack{l_2=1\\l_2\neq k}}^{p}\Lambda_{l_2j}\omega_{kl_2}\frac{n^*_k}{n^*_{l_2}}\pi^*_{hk}}{\Big(\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}\Big)\Big(\mu+\sum_{\substack{k_2=1\\k_2\neq k}}^{p}\omega_{kk_2}\Big)} \\
&+ \frac{\sum_{\substack{l_2=1\\l_2\neq k}}^{p}\sum_{\substack{l_3=1\\l_3\neq l_2}}^{p}\Lambda_{l_3j}\omega_{kl_2}\omega_{l_2l_3}\frac{n^*_k}{n^*_{l_3}}\pi^*_{hk}}{\Big(\mu+\sum_{\substack{k_1=1\\k_1\neq k}}^{p}\omega_{kk_1}\Big)\Big(\mu+\sum_{\substack{k_2=1\\k_2\neq k}}^{p}\omega_{kk_2}\Big)\Big(\mu+\sum_{\substack{k_3=1\\k_3\neq l_3}}^{p}\omega_{l_3k_3}\Big)}+\ldots\Bigg)\Bigg)+\sum_{\substack{k=1\\k\neq i}}^{p}\omega_{ki}\frac{n^*_k}{n^*_i}\pi^*_{hk}\Bigg].
\end{aligned}$$

Thus, if we define the $p\times p$ matrix $\mathbf{M}$ as:

$$\boldsymbol{M}=\boldsymbol{I}+(\sigma(1-\delta)+\sigma\alpha\delta)\boldsymbol{A}, \tag{7.58}$$

this implies that:

$$\begin{aligned} \pi^*_{hi} &= \left[1 - (\boldsymbol{M}\boldsymbol{\pi}^*_h)_i\right] \sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk} \\ &= \left[1 - (\boldsymbol{M}\boldsymbol{\pi}^*_h)_i\right] \left(\boldsymbol{Q}^*\boldsymbol{\pi}^*_h\right)_i, \end{aligned} \tag{7.59}$$

where $\boldsymbol{\pi}^*_h = (\pi^*_{h_1}, \pi^*_{h_2}, \ldots, \pi^*_{h_p})$.

Now we are in position to complete our proof and show that if $R_0 > 1$ there is at least one positive equilibrium solution. We can rewrite the equation (7.59) in the form:

$$x_i = [1 - (\boldsymbol{M}\boldsymbol{x})_i](\boldsymbol{Q}^*\boldsymbol{x})_i \qquad\qquad i = 1, 2, \ldots p. \tag{7.60}$$

Here $\boldsymbol{x} = \boldsymbol{\pi}^*_h$. This is considered as the key defining equation. We follow a similar argument as in the proof of Theorem 3.1.8.

Theorem 7.4.7. *Assume that $R_0 > 1$. Then the equation (7.60) has at least one positive non-zero solution corresponding to an equilibrium.*

Proof. Let us denote C to represent the cone of positive vectors:

$$C = \{\boldsymbol{x} = (x_1, x_2, \ldots, x_p) : x_1 \geq 0, x_2 \geq 0, \ldots, x_p \geq 0\}.$$

C is clearly a cone: if $\boldsymbol{x} \in C$ then $\alpha\boldsymbol{x} \in C$ for all $\alpha > 0$.

We use Theorem 1.6 of Gatica & Smith (1977) applied to the operator $T : C \longrightarrow$

C given by the equation:

$$T_i(\boldsymbol{x}) = \begin{cases} \left[1 - (\boldsymbol{M}\boldsymbol{x})_i\right]\left(\boldsymbol{Q}^*\boldsymbol{x}\right)_i \exp\left(-\sum_{k=1}^{p} \max\left(x_k - 1, 0\right)\right) & \text{if } (\boldsymbol{M}\boldsymbol{x})_i \leq 1, \\ 0 \qquad\qquad \text{otherwise,} & \text{for } i = 1, 2, \ldots p. \end{cases} \tag{7.61}$$

We need to introduce the factor:

$$\exp\left(-\sum_{k=1}^{p} \max(x_k - 1, 0)\right),$$

to ensure that $T(\boldsymbol{x})$ is compact. Theorem 1.6 of Gatica & Smith (1977) states:

Theorem 7.4.8. *Let $T : C \longrightarrow C$ be a compact continuous operator acting on a Banach space, such that $T(\boldsymbol{0}) = \boldsymbol{0}$ and T is Fréchet differentiable at $\boldsymbol{x}$=$\boldsymbol{0}$ in the direction of the cone. Assume that T satisfies:*

(a) *$T'(\boldsymbol{0})$, the Fréchet derivative of T at $\boldsymbol{x}$=$\boldsymbol{0}$, has an eigenvector $\boldsymbol{x} \in C$ corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C; and*

(b) *there exists an $R > 0$ such that if $\boldsymbol{x} \in C$ with $|\boldsymbol{x}| = R$ and $T(\boldsymbol{x}) = \mu\boldsymbol{x}$ then $\mu \leq 1$.*

Then T has a non-zero fixed point $\boldsymbol{x}_0 \in C$ with $|\boldsymbol{x}_0| \leq R$.

In order to apply this theorem we need to prove the following:

(a) *$T : C \longrightarrow C$ is a continuous compact operator;*

(b) *$T'(\boldsymbol{0})$ has an eigenvector $\boldsymbol{x} \in C$ corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C; and*

(c) *there exists an* $R > 0$ *such that if* $\boldsymbol{x} \in C$ *with* $|\boldsymbol{x}| = R$ *and* $T(\boldsymbol{x}) = \mu \boldsymbol{x}$ *then* $\mu \leq 1$.

Proof. We start our proof by showing that $T(\boldsymbol{x}) : C \longrightarrow C$ is a continuous compact operator. Clearly $T(\boldsymbol{x})$ is continuous. To show compactness note that as $|\boldsymbol{x}| \longrightarrow \infty$ some component x_l of $\boldsymbol{x}$ must tend to infinity, hence $\max_{l=1,2,\ldots p} |x_l| \longrightarrow \infty$. For $\max_{l=1,2,\ldots p} |x_l| > 1$, we deduce that for $i = 1, 2, \ldots p$

$$\begin{aligned} 0 \leq T_i(\boldsymbol{x}) &\leq \sum_{j=1}^{p} \boldsymbol{Q}^*_{ij} x_j \; e^{-\sum_{k=1}^{p} \max(x_k - 1, 0)}, \\ &\leq \sum_{j=1}^{p} \boldsymbol{Q}^*_{ij} e \max_l |x_l| \; e^{-\max_{l=1,\ldots p} |x_l|} \\ &\longrightarrow 0, \qquad \text{as} \qquad \max_{l=1,\ldots p} |x_l| \longrightarrow \infty. \end{aligned}$$

Thus for given $\epsilon > 0$, there exists R such that for $|\boldsymbol{x}| > R$:

$$|T(\boldsymbol{x})|^2 = \sum_{i=1}^{p} T_i(\boldsymbol{x})^2 \leq \epsilon.$$

Choosing $\epsilon = 1$ gives:

$$\exists \; R_1 \;\; \text{such that} \;\; \text{if} \;\; |\boldsymbol{x}| \geq R_1, \;\; |T(\boldsymbol{x})| \leq 1.$$

Hence $T(\boldsymbol{x})$ is bounded outside the region $|\boldsymbol{x}| \leq R_1$. But $|\boldsymbol{x}| \leq R_1$ is bounded. Hence $T(\boldsymbol{x})$ is bounded for all $\boldsymbol{x} \in C$. Thus $T(\boldsymbol{x})$ is a compact operator.

To prove the second condition (b) note that in a small neighbourhood of $\boldsymbol{x} = \boldsymbol{0}$:

$$T_i(\boldsymbol{x}) = \left[1 - (\boldsymbol{M}\boldsymbol{x})_i\right] \left(\boldsymbol{Q}^* \boldsymbol{x}\right)_i \qquad \text{for} \quad i = 1, 2, \ldots p.$$

So $T(\boldsymbol{x})$ is differentiable at $\boldsymbol{x} = \mathbf{0}$ with derivative:

$$T'(\mathbf{0}) = \left.\frac{\partial T_i}{\partial x_j}\right|_{\boldsymbol{x}=\mathbf{0}} = Q^*_{ij},$$

(b) states that $T'(\mathbf{0})$ has an eigenvector $\boldsymbol{x} \in C$ corresponding to eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\mathbf{0})$ with corresponding eigenvector in C. The proof follows the proof of Lemma 3.1.13.

The last condition we require is to show that there exists $R > 0$ such that if $\boldsymbol{x} \in C$ with $|\boldsymbol{x}| = R$ and $T(\boldsymbol{x}) = \mu\boldsymbol{x}$, then $\mu \leq 1$. This follows by a similar argument to the proof of Lemma 3.1.14.

Hence the operator $T : C \longrightarrow C$ has a non-zero fixed point $\boldsymbol{x}_0 \in C$. As $T(\boldsymbol{x}_0) = \boldsymbol{x}_0$ if $x_{0k} > 1$ for some $k \in \{1, 2, \ldots p\}$ then:

$$\left(M\boldsymbol{x}_0\right)_k \geq x_{0k} > 1,$$

so $T_k(\boldsymbol{x}_0) = 0$ which contradicts $T_k(\boldsymbol{x}_0) = x_{0k} > 1$. Hence $0 \leq x_{0k} \leq 1$

$$x_{0k} = T_k(\boldsymbol{x}_0) = \left[1 - (\boldsymbol{M}\boldsymbol{x}_0)_k\right]\left(\boldsymbol{Q}^*\boldsymbol{x}_0\right)_k,$$

for $k = 1, 2, \ldots p$, so $\boldsymbol{x}_0$ satisfies (7.60) which also has at least one non-zero positive equilibrium solution. This completes the proof of Theorem 7.4.7. □

We attempted to show the uniqueness of the non-zero endemic equilibrium if $R_0 > 1$. However we could not show this. The attempt at proof goes as follows:

Lemma 7.4.9. *Suppose that* $\pi^*_{h\bar{k}} > 0$ *for some* $\bar{k}$ *and for each* i, k $\lambda_i > 0$ *and* $\exists j_0$ *with:*

$$P_{ij_0}(1 - \phi_{ij_0})\Lambda_{kj_0} > 0,$$

then for any biologically feasible solution to equations (7.12) – (7.20) $\pi^*_{hi} > 0$ *for* $i = 1, 2, \ldots p$. *Also*

$$(\boldsymbol{Q}^*\boldsymbol{\pi}^*_h)_i = \sum_{j=1}^{q} Q^*_{ij}\pi^*_{hj} > 0.$$

Proof. As $\pi^*_{hk} > 0$ from the equilibrium versions of equation (7.18) and (7.19) we have:

$$\beta^*_{hj_0} = \frac{\sum_{i=1}^{p} \Lambda_{ij_0}\pi^*_{hi}}{\sum_{i=1}^{p} \Lambda_{ij_0}\pi^*_{hi} + \tau_{j_0}} > 0.$$

But from the equilibrium version of equation (7.12) for each $i = 1, 2, \ldots p$ if $\pi^*_{xi} = 0$ then:

$$0 = \mu + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ki}\frac{n^*_k}{n^*_i} \geq \mu > 0.$$

This is a contradiction so $\pi^*_{xi} > 0$. Hence from adding the equilibrium version of equations (7.14) and (7.15) if $\pi^*_{hi} = 0$ then:

$$\begin{aligned} 0 &= (\pi^*_{xi} + \pi^*_{x_1 i}) \sum_{j=1}^{q} \lambda_i P_{ij}(1 - \phi_{ij})(\alpha_h\beta^*_{hj} + \alpha_y\beta^*_{yj}) + \sum_{\substack{k=1 \\ k\neq i}}^{p} \omega_{ki}\pi^*_{hk}\frac{n^*_k}{n^*_i}, \\ &\geq \pi^*_{xi}\lambda_i P_{ij_0}(1 - \phi_{ij_0})\alpha_h\beta^*_{hj_0} > 0. \end{aligned}$$

This is a contradiction. Hence $\pi^*_{hi} > 0$. The fact that $(\boldsymbol{Q}^*\boldsymbol{\pi}^*_h)_i > 0$ follows from:

$$(\boldsymbol{Q}^*\boldsymbol{\pi}^*_h)_i = \frac{\sum_{j=1}^q \lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\alpha_h \sum_{k=1}^p \Lambda_{kj}\pi^*_{hk} + \alpha_y \sum_{k=1}^p \Lambda_{kj}\pi^*_{yk}}{\sum_{l=1}^p \Lambda_{lj}+\tau_j}\right) + \sum_{\substack{k=1 \\ k\neq i}}^p \omega_{ki}\frac{n^*_k}{n^*_i}\pi^*_{hk}}{\mu+\sigma+\sum_{k=1}^p \omega_{ik} + \sum_{j=1}^q \lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\alpha_h \sum_{k=1}^p \Lambda_{kj}\pi^*_{hk} + \alpha_y \sum_{k=1}^p \Lambda_{kj}\pi^*_{yk}}{\sum_{l=1}^p \Lambda_{lj}+\tau_j}\right)},$$

and

$$\sum_{j=1}^q \lambda_i P_{ij}(1-\phi_{ij})\left(\frac{\alpha_h \sum_{k=1}^p \Lambda_{kj}\pi^*_{hk} + \alpha_y \sum_{k=1}^p \Lambda_{kj}\pi^*_{yk}}{\sum_{l=1}^p \Lambda_{lj}+\tau_j}\right) > 0.$$

Now the argument proceeds as in the proof of Lemma 3.1.15. let $(\tilde{\pi}^*_{h1}, \tilde{\pi}^*_{h2}, \ldots, \tilde{\pi}^*_{hp})$ and $(\pi^*_{h1}, \pi^*_{h2}, \ldots, \pi^*_{hp})$ be two distinct non-zero equilibrium solutions. This implies that $\pi^*_{hi_0} \neq \tilde{\pi}^*_{hi_0}$ for some $i_0 \in 1, 2, \ldots p$. So, $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} \neq 1$, thus either $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} > 1$ or $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} < 1$. If $\tilde{\pi}^*_{hi_0}/\pi^*_{hi_0} < 1$ then we can redefine our parameters to allow us to assume without loss of generality that:

$$\frac{\tilde{\pi}^*_{h1}}{\pi^*_{h1}} > 1,$$

and

$$\frac{\tilde{\pi}^*_{h1}}{\pi^*_{h1}} > \frac{\tilde{\pi}^*_{hj}}{\pi^*_{hj}} \qquad \forall\ j = 2, 3, \ldots p.$$

Then we have:

$$\pi^*_{h1} = \left[1 - (\boldsymbol{M}\boldsymbol{\pi}^*_h)_1\right](\boldsymbol{Q}^*\boldsymbol{\pi}_h)_1.$$

$$0 = -\tilde{\pi}^*_{h1} + \left[1 - (\boldsymbol{M}\tilde{\boldsymbol{\pi}}^*_h)_1\right](\boldsymbol{Q}^*\tilde{\boldsymbol{\pi}}_h)_1,$$

and

$$0 = -\pi^*_{h1} + \left[1 - (\boldsymbol{M}\boldsymbol{\pi}^*_h)_1\right](\boldsymbol{Q}^*\boldsymbol{\pi}_h)_1.$$

These equations imply that:

$$1 \;>\; (\boldsymbol{M}\boldsymbol{\pi}^*_h)_1,$$

and

$$1 \;>\; (\boldsymbol{M}\tilde{\boldsymbol{\pi}}^*_h)_1.$$

Now multiply the sides of the first equation by $\pi^*_{h1}/\tilde{\pi}^*_{h1}$ we deduce that:

$$\begin{aligned} 0 &= -\pi^*_{h1} + \left[1 - (\boldsymbol{M}\tilde{\boldsymbol{\pi}}^*_h)_1\right] \sum_{k=1}^{p} Q^*_{1k}\tilde{\pi}_{hk}\frac{\pi^*_{h1}}{\tilde{\pi}^*_{h1}}, \\ &< -\pi^*_{h1} + \left[1 - (\boldsymbol{M}\tilde{\boldsymbol{\pi}}^*_h)_1\right] \sum_{k=1}^{p} Q^*_{1k}\pi^*_{hk}, \end{aligned}$$

as $\tilde{\pi}^*_{hk}\frac{\pi^*_{h1}}{\tilde{\pi}^*_{h1}} < \pi^*_{hk}$ for $k = 2, 3, \ldots p$ and

$$0 < 1 - (\boldsymbol{M}\tilde{\boldsymbol{\pi}}^*_h)_i.$$

However the proof breaks down now as before we could deduce that:

$$0 < 1 - P\tilde{\pi}^*_{hi} < 1 - P\pi^*_{hi},$$

but here we cannot deduce that:

$$1 - (\boldsymbol{M}\tilde{\boldsymbol{\pi}}^*_h)_i < 1 - (\boldsymbol{M}\boldsymbol{\pi}^*_h)_i.$$

Thus we are not able to show the uniqueness of the non-zero endemic equilibrium when $R_0 > 1$. □

It is often thought it will be more effective mathematical modelling if we could present some numerical simulations and numerical results with formulated and estimated parameters, to support our theoretical results that we achieved earlier. Thus, we shall display these results in the next section with some simulation of the total proportions of infected addicts, needles and antibody positive addicts in both cases where $R_0 \leq 1$ and $R_0 > 1$.

7.5 Numerical Results and Simulations

Theoretical models improved our understanding of the general behaviour of HCV under more realistic assumptions where addicts are allowed to move from one state to others. This assumption makes some of our previous parameters variable over time. One of these is the number of addicts in different groups. In our simulations for simplicity, we assume that we have two groups of addicts, the first one has number of addicts n_1 and the second has number of addicts n_2. The rate that addicts in group 1 move to group 2 is assumed to be ω_{12}, and similarly the rate that addicts move from group 2 to group 1 is assumed to be ω_{21}.

In the survey of NESI (2012), it has been found that the percentage of respondents who injected in the last six months but not in the last month in 2010 is 5%. Hence 1% per month injected with a needle that had previously been used by someone else. So per year this percentage will be 12% of addicts used a needle that has been used by another addict. Recall that we suppose that the total number of addicts in Glasgow is about $n = 9,000$, thus we choose arbitrarily that the number of addicts in group one is $n_1 = 7,000$ where in group two it is $n_2 = 2,000$. Moreover,

we assume that $\omega_{12} = 0.12$ per year and $\omega_{21} = 0.098$ per year. Thus the following system of differential equations describes the number of addicts in group 1 and group 2:

$$\frac{dn_1}{dt} = n_2\omega_{21} - n_1\omega_{12}, \tag{7.62}$$

$$\frac{dn_2}{dt} = n_1\omega_{12} - n_2\omega_{21}. \tag{7.63}$$

We assume that there is only one shooting gallery so $P_{i1} = 1$ for $i = 1, 2$. In the case where there are two groups of addicts $p = 2$ and the same numerical estimation parameters in our previous simulation results we deduce that the basic reproductive number is the spectral radius of the 2×2 matrix $\mathbf{Q}$. From equations (7.25) and (7.26) we have:

$$Q_{1k} = \sum_{j=1}^{q} \frac{\Lambda_{kj}(1-\phi_{kj})}{\sum_{k=1}^{p}\Lambda_{kj} + \tau_j} \left[\frac{\alpha_h \lambda_1 P_{1j}}{\mu + \sigma + \omega_{12}} + \frac{\alpha_y(1-\delta)\sigma}{\mu+\sigma+\omega_{12}} \left[\frac{\lambda_1 P_{1j}(\mu+\omega_{21})}{\mu(\mu+\omega_{12}+\omega_{21})} + \frac{\lambda_2 P_{2j}\omega_{12}}{\mu(\mu+\omega_{12}+\omega_{21})} \right] \right] + I(k=2)\frac{\omega_{12}}{\mu+\sigma+\omega_{12}}, \tag{7.64}$$

where

$$I(k=2) = \begin{cases} 1 & \text{if } k = 2\ , \\ 0 & \text{otherwise.} \end{cases}$$

Also

$$Q_{2k} = \sum_{j=1}^{q} \frac{\Lambda_{kj}(1-\phi_{kj})}{\sum_{k=1}^{p}\Lambda_{kj}+\tau_j}\left[\frac{\alpha_h\lambda_2 P_{2j}}{\mu+\sigma+\omega_{21}} + \frac{\alpha_y(1-\delta)\sigma}{\mu+\sigma+\omega_{21}}\left[\frac{\lambda_2 P_{2j}(\mu+\omega_{12})}{\mu(\mu+\omega_{12}+\omega_{21})}\right.\right.$$

$$\left.\left. + \frac{\lambda_1 P_{1j}\omega_{21}}{\mu(\mu+\omega_{12}+\omega_{21})}\right]\right] + I(k=1)\frac{\omega_{21}}{\mu+\sigma+\omega_{21}}. \quad (7.65)$$

Now recall that:

$$\mathbf{Q} = \begin{bmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{bmatrix}.$$

By solving the quadratic equation $(Q_{11}-\lambda)(Q_{22}-\lambda)-Q_{12}Q_{21}=0$. In these numerical results, the parameters are estimated as $\lambda_1 = 65$ per year, $\lambda_2 = 10$ per year, $\omega_{21} = 0.12$ per year, $\omega_{12} = 0.098$ per year, $\phi = 0.255$, $\tau = 133$ per year, $m = 8,982$, $n_1 = 7,000$ and $n_2 = 2,000$. These values gives us that $R_0 = 0.873$. At time $t = 0$ and for $i = 1, 2$, $\pi_{x_1 i}(0) = 0.99, \pi_{xi}(0) = \pi_{h_2 i}(0) = \pi_{yi}(0) = \pi_{zi}(0) = 0$ and $\pi_{h_1 i}(0) = 0.01$. So 99% of addicts were not infected while 1% of addicts were in the acute h_1 stage. Similarly for the fractions of infectious needles at time $t = 0$ for $j = 1$, $\beta_{h_1 1}(0) = \beta_{h_2 1}(0) = \beta_{y1}(0) = 0$. To simulate our extended model we use the Berkeley Madonna package and the differential equation system (7.12) – (7.20), with parameters estimated as above, $\lambda_1 = 65$ per year, $\lambda_2 = 10$ per year, $\omega_{21} = 0.12$ per year, $\omega_{12} = 0.098$ per year gives us $R_0 = 0.9249 < 1$.

Figure 7.1 shows simulation of the extended model under the assumption of addicts moving in and out of groups. Clearly we can see that the disease dies out in both addicts and needles and the model tends to the equilibrium after nearly 70

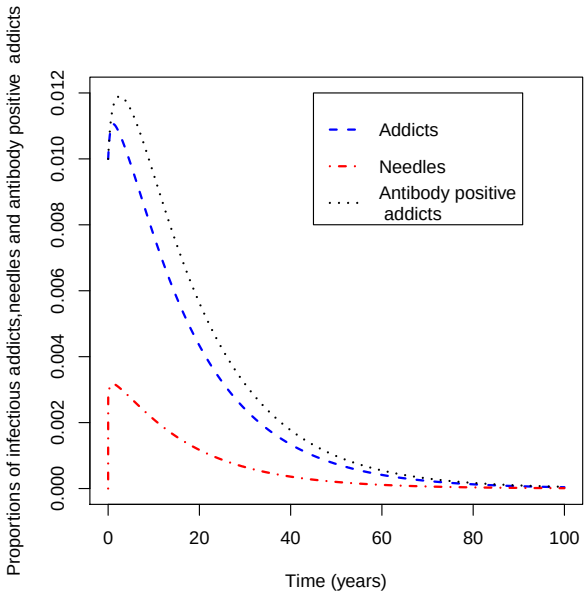


Figure 7.1: Total proportion of infectious addicts, needles and antibody positive addicts who are allowed to move in and out of groups when $R_0 = 0.9249 < 1$.

years where the simulation is performed over 100 years. As we mentioned in this case we found that $R_0 < 1$ which is compatible with our theoretical results which we mentioned earlier. Next, we will simulate our extended model in the case where $R_0 > 1$.

One of the important aspects is to understand the model dynamic if R_0 exceeds unity. Thus we keep the rate of moving from one group to another but we increase the needle sharing rate between the two groups. This assumption is estimated to be $\lambda_1 = 150$ per year and $\lambda_2 = 50$ per year, keeping all other parameters estimated before including ω_{12} and ω_{21}. The expression given by the spectral radius of the matrix $\mathbf{Q}$ given in equations (7.25) and (7.26) with these values gives us that $R_0 = 3.692 > 1$. Our simulation presents this result in Figure 7.2 where the infectious addicts and needles achieve the equilibrium state where the disease persists

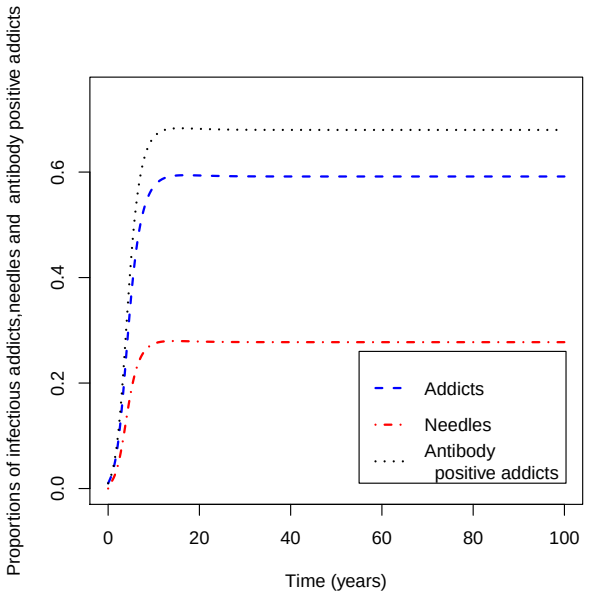


Figure 7.2: Total proportion of infectious addicts, needles and antibody positive addicts who are allowed to move in and out of groups when $R_0 = 3.692 > 1$.

as $R_0 > 1$. Numerical simulations support the hypothesis that there is a unique equilibrium for $R_0 > 1$.

7.6 Conclusion

In our basic model of the spread of HCV among drug users where there are p groups of addicts, we have assumed that the number of addicts in each group is constant. In fact this assumption is made for simplicity, nevertheless to be more realistic we developed our basic model to a model where addicts are allowed to move in and out of groups. This chapter set out to investigate the heterogeneity of the spread of HCV among addicts in different groups and needles in shooting galleries under the new assumption, to analyse and understand the effects of the group size dynamics.

First, we introduced the differential equation system (7.1) which describe the number of addicts in each group. We also derived the differential equations of the total number of susceptible, second and subsequent time susceptible, acutely infected h_1-class, acutely infected h_2-class, chronically infected individuals and immune individuals in each group over time. These equations were used to obtain the extended model equations system (7.12) - (7.20) with the suitable initial conditions.

Then, we defined the basic reproductive number R_0 and gave an expression to calculate this ratio. Both basic and extended models have the same disease-free equilibrium. Moreover, R_0 can be calculated as it is the largest eigenvalue of the $p \times p$ matrix $\mathbf{Q}$, where Q_{ik} is defined by the formula (7.27). We expect that the disease cannot invade the groups of addicts and shooting galleries if $R_0 < 1$, whereas if $R_0 > 1$ the disease can invade the population and the number of infected individuals grows.

The main purpose of this chapter was to determine the effect of group size dynamics on the spread of HCV. Thus, we analysed this model through two main theorems, the first theorem stated that there is a unique positive equilibrium distribution, and the second theorem the system of group size dynamic interaction (7.1) tends to that unique equilibrium distribution. These theorems are proved by using continuous time Markov Chain processes and considered a p-dimensional Markov process representing the probability distribution at time t of a single individual who starts in a given group. Considering a collection of n addicts starting in different groups each following this Markov process gives the group size dynamic equations

discussed earlier. For the second theorem we discussed the 2×2 case first followed by the $p \times p$ case. We have also discussed the equilibrium and stability of the steady states of our model. This model has at least two non-negative equilibrium points namely: the disease-free equilibrium and a non-zero endemic equilibrium. The extended model has a unique disease-free equilibrium, which is globally asymptotically stable and hence unique if $R_0 \leq 1$. Moreover, the model has at least one positive non-zero endemic equilibrium if $R_0 > 1$.

Later, we presented some numerical simulations and numerical results with formulated and estimated parameters, to support our theoretical results that we achieved earlier. Two groups of addicts 1 and 2 have been considered with addicts moving in and out of groups at two different rates ω_{12} and ω_{21}. Other parameters are estimated as in the basic model and used to compute R_0. Two interesting graphs of the extended model have been displayed, showing the total proportions of infectious addicts, needles and antibody positive addicts. The first, Figure 7.1, was when $R_0 < 1$ and the second, Figure 7.2, was when $R_0 > 1$. These simulations are based on the differential equations describing group size dynamics and heterogeneity of needle sharing between different groups. As expected the simulations confirm that the disease dies out if $R_0 < 1$ and takes off if $R_0 > 1$.

Chapter 8

Conclusions and Further Work

As pointed out earlier in this thesis, HCV is a global disease. Since Hepatitis C virus was discovered, injecting drug users have been considered as being at the highest risk of infection with HCV. Mathematical modelling techniques are being used by health organisations worldwide to help understand the likely impact that intervention strategies, treatment options and combinations of these have on the prevalence and incidence of HCV in the drug addict population. Thus our thesis highlighted the transmission of this disease among injecting drug users where they are sharing needles in shooting galleries. We developed a deterministic, compartmental mathematical model to approximate the spread of HCV in an injecting drug user population by Corson et al. (2012). In particular, we were interested in the effect of heterogeneity of the population of addicts who share injecting needles and syringes. In the following sections, we outline briefly the work contained in this thesis.

A better understanding of the core epidemiologic concepts will help researchers to identify and optimize prevention and control diseases. Hence we began our thesis by a review of the epidemiology of HCV infection, its discovery and transmission routes.

This was followed by a brief discussion about HCV treatment and global prevalence of HCV. We also outlined the prevalence of HCV worldwide among injecting drug users, as well as the model structure and discussed the basic reproductive number R_0 as the fundamental parameter which determines the disease dynamic and behaviour. As our thesis studies the impact of heterogeneity on the prevalence of HCV, we discussed this concept and reviewed some examples of heterogeneity models of infectious diseases. Moreover, we reviewed two models, which approximate the spread of HCV, as they are the most relevant to our work. The first one is by Vickerman et al. (2007), and the second one is by Corson et al. (2012).

8.1 Using a Heterogeneous Mathematical Model for the Spread of HCV

In Chapter Two we developed accurate models of the spread of HCV and discussed a mathematical model of the impact of heterogeneity on HCV prevalence among addicts and needles. A system of differential equations has been derived to describe the progress of the disease among injecting drug users and needles in shooting galleries. These equations were set up using clearly defined hypotheses and biological parameters. The heterogeneity came from assuming that we had p of groups of addicts, who shared needles in q shooting galleries according to different sharing rates, visiting probabilities and the other parameters. Six epidemiological classes of infectivity are studied, first time x_i susceptible, x_{1i} second time susceptible, h_{1i} acutely infected, h_{2i} acutely infected, y_i chronic and z_i immune stages for $i = 1, 2, \ldots p$. The differential equations for the needles contained three different stages of infectivity h_{1j} acutely

infected, h_{2j} acutely infected and y_j chronically infected for $j = 1, 2, \ldots q$.

8.2 Estimation of the Basic Reproductive Number

For epidemiology models the basic reproduction number R_0 for an infectious disease is defined as the expected number of secondary cases caused by a single newly infectious case entering a disease-free population at equilibrium. In Chapters Two and Six we discussed this important number as a key parameter which determined the general progress of HCV among addicts and needles. We derived an expression for R_0, then we studied special scenarios that minimised R_0. In particular, three special cases were presented:

- The effect on R_0 of addicts in different groups visiting shooting galleries at different rates.
- Optimal allocation of limited needle exchange effort between different shooting galleries.
- Optimal allocation of limited needle cleaning effort between different groups of addicts and shooting galleries.

In Chapter Six we discussed numerical illustrations of these special cases followed by some plots to illustrate the relationship between the parameters and R_0. These results revealed that it might be possible to control the disease by considering minimisation of R_0.

8.3 Analytical Results and Stability

In Chapter Three we conducted an extensive mathematical analysis of the model. We found that the behaviour of our model was governed by R_0, with $R_0 = 1$ a critical threshold for endemic HCV prevalence. We found that if $R_0 \leq 1$ and HCV is initially present in addicts groups and needles, then the model tends towards a globally stable disease-free equilibrium where HCV has been eliminated in all addicts groups and shooting galleries. We also discussed persistence of the disease. If $R_0 > 1$ and disease is initially present in at least one group of addicts or at least one shooting gallery, then provided that an irreducibility condition is satisfied then disease will ultimately persist in all groups of addicts and all needles. Moreover, the ultimate lower bound for the level of HCV in infected needles and addicts depends only on the model parameters not the initial conditions. Additionally if $R_0 > 1$ and the same irreducibility condition is satisfied then we showed that there was a unique endemic equilibrium.

8.4 Simulation

Numerical simulations using the heterogeneity HCV transmission model, presented in Chapters Four and Five were conducted to verify the analytical results and estimate the level of intervention required to give $R_0 \leq 1$ and therefore eliminate HCV from all addicts groups and needles. Extensive simulations were conducted and these simulations confirmed our analytical results which were presented in Chapter Three. We simulate the heterogeneity of sharing rates in Chapter Four, alongside with the assumption that the model parameters are all homogeneous. The sharing rates were

calculated using survey data collected by HPS (Hutchinson et al., 2000) during the early 1990s for drug users in Glasgow, in particular we used the data from 1990 and 1993.

In Chapter Four we have assumed that there is one shooting gallery where all addicts share needles. We divide the addict population into different numbers of groups with different sharing rates. As the number of groups increased R_0 also increased. The initial rate of increase of the level of disease also increased with the number of groups as did the endemic equilibrium prevalence of HCV amongst needles. However, both the endemic equilibrium proportion of HCV amongst addicts and the endemic equilibrium number of HCV antibody positive addicts show the opposite pattern. There as the number of groups increased the endemic prevalence of HCV amongst addicts and the endemic equilibrium number of HCV antibody positive addicts decreases as the number of groups increased.

In Chapter Five we have considered the heterogeneity of visiting shooting galleries. In the light of the lack of data of the probabilities of shooting galleries visiting probabilities, we estimated these parameters. We started our discussion with the assumption that we have a homogeneous society of addicts and two shooting galleries. An explicit expression for R_0 is given, and it exceeded one in each of the three models considered. These models are set up with three different set of visiting probabilities. In each model we presented a plot of total proportions of infectious addicts and needles against time. Then a general comparison of these models is given of the total proportions of infectious addicts and the antibody positive addicts in the

three models. These figures showed that there although the three models have three very different sets of shooting galleries visiting probabilities, these models behave similarly.

8.5 Use of Extended Mathematical Model of HCV Prevalence

Our next target was to extend our basic mathematical model by assuming that addicts are allowed to move in and out of groups. This assumption is more realistic and makes the model substantially more complicated. In Chapter Seven, we covered the epidemiologic and dynamical concepts for preventing and controlling HCV among injecting drug users, where we introduced the differential equation system that describes the spread of HCV in the extended model with the suitable initial conditions. Then, we defined the basic reproductive number R_0. We expected that the disease cannot invade the groups of addicts and shooting galleries if $R_0 \leq 1$, whereas if $R_0 > 1$ the disease can invade the population and the number of infected individuals grows.

The main purpose of Chapter Seven, was to determine the effect of group size dynamics on the spread of HCV. Thus, we analysed this model through two main theorems, the first theorem stated that there is a unique positive equilibrium distribution for group sizes, and in the second theorem the system of group size dynamic interaction (7.1) tends to that unique equilibrium distribution. These theorems are proved by using continuous time Markov Chain processes and considered a p-dimensional

Markov process representing the probability distribution at time t of a single individual who starts in a given group. Then, we looked at the stability of the equilibrium solution of the extended model system. We proved that if $R_0 \leq 1$ then the extended model system has a disease-free equilibrium solution which is a globally asymptotically stable. If $R_0 > 1$ there is a non-zero equilibrium solution.

We concluded this discussion by presenting some numerical simulations and numerical results with formulated and estimated parameters, to support our theoretical results that we achieved earlier. These simulations were based on the differential equations describing group size dynamics and heterogeneity of needle sharing between different groups. As expected the simulations confirmed that the disease dies out if $R_0 \leq 1$ and takes off if $R_0 > 1$.

8.6 Practical Use of Results in Disease Control Policy

Throughout this thesis we have aimed to study reducing the spread of the disease amongst injecting drug users. Recall that the basic reproduction rate R_0, is used to measure the transmission potential of a disease. It is defined as the expected number of secondary infections produced by a typical case of a newly infected individual entering a completely susceptible population at equilibrium (Dietz, 1993). One of the main results that we proved earlier states that if R_0 is less than or equal to one, then HCV will die out in all addicts groups and all shooting galleries. For this reason, it is important to control the disease by making R_0 as small as it can be.

The model can be used to evaluate the impact of control strategies on the spread of the disease. Typical control strategies are needle exchange, needle cleaning and educating addicts to reduce their needle sharing rates. We already discussed in Chapter Four how to estimate realistic parameter values for the model. So for example: if we estimated all other parameters we could plot R_0 against the common needle exchange rate τ (in all shooting galleries) and find the critical value that just eliminated the disease or if we chose to apply different needle exchange rates in different shooting galleries, we could calculate which combination of those needle exchange rates reduce R_0 to one and thus just eliminated disease.

Similarly we could use the results to determine policy on distribution of needle cleaning kits. If the needle cleaning probability was the same for all groups of addicts in all shooting galleries, we could calculate the critical needle cleaning probability that just eliminated the disease, or what combination of needle cleaning probabilities would eliminate the disease. Similarly, we could look at the effect of education of people who inject drugs to see what needle sharing in different shooting galleries or combination of different sharing rates in different shooting galleries eliminated disease.

Alternatively we could look at combinations of needle exchange rates, needle sharing rates and see what combination of those would eliminate disease. Another possible application is to look at the effect on reduuction of endemic disease levels when an intervention is not suffecicent to eliminate disease. For example: we could

look at which of given reduction in needle sharing, a given increase in needle exchange or a given increase in needle cleaning probabilities would reduce endemic disease levels amongst addicts the most. Some examples of this for a simpler homogeneously mixing model are given by Corson (2012).

The results on optimal allocation of control effort in Chapter Two can tell us which shooting galleries it is most effective to target for needle exchange effort and which groups of addicts and shooting galleries it is most effective to target to eliminate disease. Some numerical illustrations of this were given in Chapter Six.

8.7 Recommendation for Further Work

Although the results presented here have demonstrated the significance of heterogeneity on the spread of HCV among addicts and needles, there are many possible areas in which the work in this thesis could be developed further. One of these recommendations is to improve the simulation results, through simulating the heterogeneity effects of the other parameters, for example the probability that an addict cleans a needle before use and the rate of needle turnover.

Regarding the models of HCV dynamics and the impact of heterogeneity, it would be interesting to investigate other characteristic parameters in social life such as the gender of injecting drug users (male or female), and how that affects the dynamics of the system in general, also paying attention to the age of addicts especially young injecting drug users (less than 30 years old). It would also be of great interest to investigate the basic reproductive number and the effective reproductive conditions

of the transmission process.

Another very interesting question would be to investigate how the heterogeneity of sharing of other injecting paraphernalia (as well as needles and syringes) would affect the progress of HCV among injecting drug users. Although we mentioned earlier that the increased risk of HCV is associated with sharing of contaminated needles and syringes, a growing body of literature suggests that infected spoons, cotton filters, the water used to prepare the drugs and other paraphernalia also act as vectors for HCV transmission (Matheï et al., 2006). As no vaccine against HCV is currently available, preventive measures like education, needle exchange and distribution of other paraphernalia are major weapons currently to hand in the war against further spread of HCV among injecting drug users.

The models discussed in this thesis assume that needles adopt the infectivity characteristics of the last addict to use them. This is the simplest possible assumption and made in other models of HIV/AIDS and hepatitis C (see for example Corson et al. (2012) and Greenhalgh & Lewis (2000)). Greenhalgh and Lewis call this the Optimistic Model Assumption. It is motivated by the assumption that the blood in the syringe is replaced by the blood of the addict. However an alternative assumption is that syringes get progressively more infectious over time as such an assumption has previously been used to model the spread of HIV/AIDS amongst injecting drug users (Lewis & Greenhalgh, 2001). This is called the Pessimistic Model Assumption. An alternative assumption would be to incorporate this into our models.

Over the past decade, treatment for HCV has been shown to be highly effective, achieving viral clearance rates (depending on genotype) of between 55 and 85% (Grebely et al., 2008). Therefore, it may be worth considering treatment in the modelling the heterogeneity of the spread of HCV. It would also be of great interest how a combination of treatment of HCV and heterogeneity, for example in needle sharing rates, may modify the spread of the disease among drug users. Also, it would be interesting to extend the model to consider two main groups of addicts, one of which is treated and the other of which is not, and investigate the dynamics of HCV progress between these groups.

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