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Modelling the Spread of Hepatitis C Virus Infection Among Injecting Drug Users in Glasgow

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Chapter 1

Introduction and thesis outline

The hepatitis C virus (HCV) is a major health problem affecting an estimated 3% of the global population (World Health Organisation 2000). Just two decades after the virus was discovered, HCV is now the leading cause of liver disease in the world (Shepard *et al.* 2005). In Scotland, as well as other resource-rich countries, the majority of infections can be attributed to a history of injecting drug use. Around 50,000 people in Scotland are infected with HCV and the overwhelming majority of these infections are amongst current or former injecting drug users (IDUs) (Hutchinson, Roy *et al.*, 2006). Services to prevent infections amongst IDUs, particularly HIV and HCV, have been around since the 1980s. Although these services appear to have been effective in preventing the transmission of HIV amongst IDUs in Scotland, they have been less effective in preventing the transmission of HCV in this population. Therefore, recent recommendations, such as those contained in the Hepatitis C Action Plan of the Scottish Government (Scottish Executive 2008b), have sought to improve intervention coverage within the IDU population and prevent the spread of HCV infection. Unfortunately, the dynamics of IDU populations and factors influencing the spread of HCV in this group are difficult to study.

Mathematical modelling techniques are increasingly being used to understand the intricate relationship between the risk behaviour of IDUs and the transmission of HCV. In addition, these techniques are being used to understand the likely impact that different intervention strategies, treatment options, diagnostic tools and combinations of these have on the healthcare burden associated with HCV.

Hence the work contained in this thesis will focus on the development and

analysis of mathematical models which approximate the spread of HCV amongst IDUs. We will use these models to obtain HCV prevalence estimates for Glasgow IDUs and examine the effect that different parameter estimates and intervention measures have on our prevalence estimates. In particular, we are interested in finding situations which lead to the eventual elimination of HCV from the Glasgow IDU population. For example, we wish to determine the number of needles and syringes that the Greater Glasgow and Clyde health board would need to distribute in order to eliminate HCV in this population. We now outline the work contained in this thesis before presenting the results of the literature search.

1.1 Thesis outline

In Chapter 2 a systematic review of the literature is presented. This review examines the evidence on three key areas of HCV transmission in the IDU population: the rate of acute HCV infection amongst IDUs who have spontaneously resolved a previous infection, the rate of chronic infection following re-infection amongst IDUs who have spontaneously resolved a previous infection, and the ability of IDUs to be re-infected with either the same or a different genotype. These are key issues to be considered when modelling HCV epidemics and the impact of intervention measures. The methods employed in the literature search along with the findings of the included studies are discussed.

In Chapter 3 a simple deterministic model that approximates the spread of HCV in an IDU population is presented. This model allows IDUs to progress through the various stages of HCV infection as well as allowing needles to exist in three infectious classes, where the infectivity of each needle is determined by the infectivity of the IDU who last used the needle. This conservative assumption makes our model optimistic compared to other possible assumptions and could be used to provide a lower bound for the fraction of IDUs and needles infected with HCV. We conduct equilibrium and stability analyses and demonstrate that the model behaviour is governed by the basic reproductive number R_0.

In Chapter 4 the parameter estimates used in our numerical simulations are discussed and the results of our numerical simulations are presented. Parameter estimates were obtained both from the literature and data sources made available by Health Protection Scotland (HPS). After a detailed discussion of the

parameter estimates, the baseline estimates used in our numerical simulations are introduced. Using these baseline parameter estimates we determine, both analytically and numerically, the threshold values that, when reached, result in HCV elimination in our population. We then examine how the uncertainty in some biological parameter estimates affects our estimates of HCV prevalence and how different scenarios affect the behaviour of our model.

In Chapter 5 we present an extension to the simple model in Chapter 3 that enables us to explicitly model the proportion of IDUs that are in the short, but highly infectious, acute stage of infection. This extension allows us to examine any differences between this model and the simple model in Chapter 3, which assumes a single acute class with a transmission probability that is an average of both the high and low transmission probabilities taken over the total length of the acute phase.

It has been well documented that the IDU population is heterogeneous in its injecting risk behaviours. For example, some IDUs report a high level of needle and syringe sharing while others do not. In Chapter 6 we present a mathematical model that separates the IDU population into two risk groups by their time since onset of injection. A mathematical analysis of the model examines the basic reproductive number, the existence and uniqueness of equilibrium solutions and the global stability of the disease free equilibrium (DFE) solution.

Chapter 7 contains the numerical simulation results for the model described in Chapter 6. These simulations examine to what extent the under-reporting of needle and syringe sharing takes place amongst Glasgow IDUs. A detailed discussion of the baseline parameter estimates precedes our numerical results.

Although the sharing of needles and syringes is considered to have the greatest contribution to HCV transmission, there is now some evidence to suggest that the sharing of injecting paraphernalia may be another source of HCV transmission. In Chapter 8 the model in Chapter 6 is extended to allow for the transmission of HCV through the sharing of injecting paraphernalia. After discussing our baseline parameter estimates we use numerical simulations to estimate the transmission probability of acute and chronic HCV through (i) filter sharing; (ii) filter and cooker sharing and (iii) filter, cooker and water sharing while assuming that the reported needle and syringe sharing rates are accurate.

In the final chapter, Chapter 9, we summarise the work contained in this

thesis, discuss any modelling work that has been published since our literature review was conducted and discuss some ideas for future work.

This completes our summary of the work contained in this thesis. The rest of this chapter is devoted to our literature survey. The first section introduces the reader to HCV and discusses some of the key biological properties of the disease as well as the treatment options that are currently available. In Section 2, we discuss HCV transmission routes and examine the risk of infection associated with each one. Since the work contained in this thesis focuses on IDUs, we pay particular attention to the risks associated with injecting drug use and any factors that can increase the risk of HCV infection for IDUs. The subsequent section examines the prevalence of HCV amongst IDUs. We begin by examining the prevalence of HCV amongst IDUs worldwide before focusing on the prevalence of HCV amongst IDUs in Glasgow. The rest of the chapter focuses on the modelling of infectious diseases. We begin by reviewing some of the techniques and concepts involved in infectious disease modelling and discuss some modelling work which highlights the valuable insights that can be obtained from infectious disease modelling. We then discuss some of the work that has been done on the spread of HIV amongst IDUs. These models have played a key role in the understanding of the risk behaviour of IDUs and the techniques used in their development and analysis can be adapted to examine the spread of HCV amongst IDUs. Finally we discuss some models of HCV spread amongst IDUs.

1.2 Background on hepatitis C virus infection

Discovered in 1989, HCV is a blood-borne, single stranded RNA virus that infects the liver cells. Current estimates suggest that 180 million people worldwide are currently infected, with around four million new infections acquired each year (World Health Organisation 2000). HCV can cause both acute and chronic infections. Acute HCV refers to first six months after initial infection where spontaneous viral clearance is possible (Hoofnagle 2002; Kamal 2008). If a patient has detectable HCV RNA after this six month period they are considered to have chronic HCV infection (Craxi *et al.* 2008). Since at least 70-80% of cases are asymptomatic (Chen and Morgan 2006; Kamal 2007) the majority of patients are unaware that they have been exposed to HCV. However, the few patients with

HCV who do display symptoms complain of fatigue, jaundice and constitutional problems (Simmonds *et al.* 1998; Gordon 2003; Mondelli *et al.* 2005). Around 50-80% of individuals fail to clear the virus and develop chronic HCV infection where they are at risk of developing severe liver disease many decades later (Seef 2002; World Health Organisation 2000; Kamal 2008). Approximately 4%-12% of community recruited patients with chronic HCV infection will develop cirrhosis, scarring of the liver tissue, over a period of 20 years (Freeman *et al.* 2001; Thein *et al.* 2008). After the development of cirrhosis, between 1% and 7% of individuals will develop hepatocellular carcinoma, a type of liver cancer, (Booth 1998; Seef 2002; Chen and Morgan 2006) and 6% will develop decompensated cirrhosis, in other words liver failure, (Kamal 2008). Risk factors for the development of chronic HCV infection include race, male gender, HIV co-infection and age at time of infection (Chen and Morgan 2006).

An important feature of the virus is the mutability of its genome which is caused by an ineffective proof reading mechanism. This results in a number of distinct but closely related viral strains. There are at least six known genotypes, 1, 2, 3, ... , and numerous subtypes, 1a, 2b, 3c, ... (Simmonds *et al.* 1993; World Health Organisation 2002; Chen and Morgan 2006). Mutations within the HCV genome are generated at a rate of approximately one mutation per genome per replication cycle (Blackard *et al.* 2008). This, combined with a viral replication cycle which produces an estimated ten trillion new virus particles each day (Neumann *et al.* 1998) explains why there is no vaccine available to protect against infection. Therefore, the future disease burden and economic burden of HCV is likely to be substantial (Wong *et al.* 2000; Buti *et al.* 2005; Hutchinson *et al.* 2005; Hutchinson, Bird *et al.* 2006).

1.2.1 Treatment of HCV infection

Treatment is available in the form of antiviral drugs. Interferon (pegylated or non-pegylated) or an interferon-ribavirin combination, taken over a 24-48 week period, can be used in the treatment of chronically infected patients. Pegylated interferon has a longer half life and slower rate of clearance than non-pegylated interferon (di Biscelglie and Hoofnagle 2002). The treatment of those with acute HCV infection is less common for many reasons. Since the majority of individu-

als with acute HCV are asymptomatic, it is rare for an acute HCV infection to be identified. Furthermore, the treatment of acute HCV infection must be balanced against the possibility of spontaneous viral clearance which could render the treatment needless and potentially harmful (Blackard *et al.* 2008). Treatment is regarded as being successful if patients achieve sustained virological response (SVR), whereby HCV RNA is undetectable in serum 24 weeks following the completion of treatment (Ghany *et al.* 2009). Although pegylated interferon-ribavirin treatment is currently the recommended treatment for chronic HCV, it comes with many side effects and is not 100% effective.

Overall, 50%-60% of patients who receive the combined interferon-ribavirin treatment attain SVR (Fried *et al.* 2002). However, the success rate of this treatment depends on HCV genotype: 41%-51% of patients with HCV genotype one will achieve SVR compared to 73%-82% of patients with HCV genotypes two and three (Manns *et al.* 2001; Hadziyannis *et al.* 2004; SIGN 2006). The optimal treatment duration for patients with HCV genotype one is 48 weeks. For HCV genotypes two and three the optimal treatment duration is 24 weeks (SIGN 2006).

With the introduction of new treatment options researchers hope that they can reduce the duration of, and side effects associated with, HCV treatment as well as increase its efficacy. Two new drug options, boceprevir and telaprevir, developed by Merck in New Jersey and Vetrex in Massachusetts, USA respectively are making their way onto the market (Gravitz 2011; Schlutter 2011). Both of these drugs will supplement the current peginterferon-ribavirin treatment option and are aimed specifically at those with HCV genotype one (Gravitz 2011).

Clinical trials involving boceprevir and telaprevir suggest that these compounds increase the rates of SVR and rapid viral response (RVR). RVR is when HCV RNA is undetectable at week four of treatment and this is a good predictor of SVR. In a trial involving chronically infected treatment-naive patients with genotype one in the United States, 250 patients were randomly allocated to four treatment groups (Asselah *et al.* 2009). Group one ($n = 17$) received treatment with telaprevir plus peginterferon-ribavirin treatment for 12 weeks. Groups two ($n = 79$) and three ($n = 79$) received the same treatment as group one followed by peginterferon-ribavirin treatment for a further 12 and 36 weeks respectively. Group 4 ($n = 75$) received the standard peginterferon-ribavirin treatment for 48

weeks. The results of these trials suggest that those receiving telaprevir as well as the standard antiviral therapy were significantly more likely to achieve RVR than those who received the standard antiviral therapy (79% vs 11% respectively, no p-value presented). In addition, those who received telaprevir during the first 12 weeks of a 48 week treatment performed better than those who underwent the standard 48 week treatment (65% vs 45% respectively). Similarly, early results from trials involving boceprevir suggest that combining this compound with current antiviral therapy for 48 weeks can nearly double the SVR rates of the standard 48 week therapy (Asselah *et al.* 2009).

1.3 Transmission routes

Injecting drug use and transfusions with unscreened blood products are regarded as the most efficient HCV transmission routes. However, sexual, and perinatal exposure as well as exposure through needle stick injury and tattooing and body piercing practices can result in the transmission of HCV infection. The following sections review the risks associated with the various known transmission routes for HCV:

1.3.1 Blood transfusion

In resource-rich countries, the screening of blood products for HCV antibodies was introduced in the early 1990s and has significantly reduced the risk of transfusion associated HCV infections (Donahue *et al.* 1992). In the United Kingdom in 2004, the chances of a post transfusion HCV infection was estimated to be 1 in 2,000,000 (Goldberg and Anderson 2004). However, in countries that lack the resources to implement blood product screening the risk of transfusion associated HCV infections remains high.

1.3.2 Vertical transmission

Mother to child transmission of HCV has been widely documented but it is uncommon. Although transmission is thought to occur in utero, the correlates of transmission remain unclear (Zanetti *et al.* 1999; World Health Organisation 2010) and the risk of infection in children born to HCV infected mothers

is between 3% and 7% (MacDonald *et al.* 1996; Simmonds *et al.* 1998; Zanetti *et al.* 1999). This risk increases significantly if the mother is co-infected with HIV, however, with the risk of HCV infection in children born to HCV-HIV co-infected mothers estimated to be between 5% and 36% (MacDonald *et al.* 1996; Zanetti *et al.* 1999).

1.3.3 Sexual exposure

Although sexual intercourse with an infected partner and multiple partners have been identified as risk factors for HCV (Terrault 2002; Shepard *et al.* 2005), the sexual transmission of HCV infection is not considered to be a primary source of new HCV infections. In the United States, sexual contact with an HCV infected person has been linked to 15-20% of reported acute HCV cases (Alter 2007). Meanwhile, a cross-sectional survey of monogamous spouses in Egypt found that the overall rate of HCV infection through sexual exposure was 6% (Magder *et al.* 2005). However, this risk was greater for those who had detectable HCV RNA and depended on whether transmission occurred from husband to wife or from wife to husband. For HCV antibody positive husbands, the probability of husband to wife transmission was 3% (95% CI 0-13%) if there was detectable HCV RNA or 0% (95% CI 0-9%) if there was no detectable HCV RNA. Similarly, for HCV antibody positive wives, the probability of wife to husband transmission was 34% (95% CI 15-49%) if HCV RNA was detectable or 10% (95% CI 0-26%) if HCV RNA was not detectable. Although HCV RNA was not detectable in some cases it does not necessarily mean that HCV has been eradicated in these individuals. It is possible that the virus still exists at low levels which would allow transmission to occur (Hoare *et al.* 2008).

While some cases of HCV infection have been related to sexual exposure, studies on the sexual transmission of HCV are limited by the potential of the confounding variable of injecting drug use or other shared items such as razors (Kamal 2008). This makes it difficult to accurately determine the risks posed by sexual exposure to HCV.

1.3.4 Needlestick injury

Needlestick injury is an important risk factor for health care workers with a risk of HCV infection between 0-10% (CDC 2001; Sulkowski *et al.* 2002; Elder and Paterson 2006) associated with such injuries; substantially greater than the corresponding risk of HIV infection (0.25%, MacDonald *et al.* 1996). The variation in risk is attributed to many different factors, including the RNA concentration of the source, the type of tissue exposed, the type of needle involved (i.e. whether hollow or solid bore needles) and the policies used to prevent the spread of occupational infections (Sulkowski *et al.* 2002; Kamal 2008).

1.3.5 Tattoo and body piercing practices

There is limited data available on the risk of HCV infection through tattoo and body piercing practices. It is possible, however, that unsterilised equipment used in unlicensed and unregulated settings such as prisons may present a risk of HCV infection. Vescio *et al.* (2008) conducted a meta-analysis of studies examining HCV in prison settings in order to analyse risk factors for HCV infection and to assess HCV seroprevalence and incidence in prison. A total of 30 studies were included in this meta-analysis, the results of which found that tattooing in prison settings was associated with HCV infection. The authors reported that the odds of being HCV positive were three times higher for inmates exposed to tattooing than those who were not exposed.

1.3.6 Injecting drug use

In resource-rich countries, where the screening of blood products is commonplace, injecting drug use is the main mode of transmission for HCV, with infection occurring through the direct or indirect sharing of needles and syringes (Thorpe *et al.* 2002; Bialek and Terrault 2006). Of the 29,903 individuals with diagnosed HCV infection in Scotland by 31st March 2011, 19,148 (64%) individuals had a known risk factor. From these 19,148 individuals, 17,042 (89%) were identified as current or former IDUs (McLeod *et al.* 2011). This figure indicates that injecting drug use is the main risk factor for HCV infection in Scotland. Other resource-rich countries are also reporting that injecting drug use accounts for the majority

of HCV infections: 67% of HCV cases in Norway (Shepard *et al.* 2005), 92.5% of cases in England (HPA 2009), 80% of cases in Australia (Dore *et al.* 2003) and 60% of cases in the United States (Alter 1999).

IDUs are more at risk of HCV than HIV and thus a greater prevalence of HCV, compared to HIV, is observed in this population (Garfein *et al.* 1998; Hagan and des Jarlais 2000). The probability of becoming infected with HCV after using an infected needle and syringe is estimated to be between 1.5%-5% whereas the corresponding risk for HIV is estimated to be between 0.34%-2% (Vickerman *et al.* 2009; Grebely and Dore 2011). Given that there are an estimated 13.2 million IDUs worldwide (Aceijas *et al.* 2004), the future burden of HCV (both disease and economic) is likely to be substantial.

1.4 Risk factors for HCV transmission amongst IDUs

In addition to the risk posed by the sharing of needles and syringes, there are a number of factors that can influence the risk of acquiring HCV infection for IDUs.

1.4.1 Recent initiates to injecting drug use

Recent initiates to injecting drug use (IDUs who are within their first year or few years of injecting drug use) are at great risk of HCV infection. Sutton *et al.* (2006) analysed the saliva samples of 5,682 IDUs who took part in voluntary unlinked anonymous surveys performed in England and Wales during 1998-2003. The authors derived maximum log likelihood estimates of the force of infection (the per capita rate at which susceptibles are infected per unit time) for HCV in IDUs and their trends over time and injecting career length. The results showed that recent initiates have an increased risk of HCV infection compared to experienced injectors. The 1999-2003 estimate for the force of infection for recent initiates was 0.1608 (95% CI 0.1314-0.1942) whereas the corresponding estimate for those injecting one year or more was 0.0526 (95% CI 0.0310-0.0863). Similar results were reported by Maher *et al.* (2007) who found that incidence for IDUs aged between 15-19 was 55.7 (95% CI 35.1-88.4) per 100 person years whereas

the incidence for IDUs aged 25 or older was 38 (95% CI 21.6-66.8) per 100 person years.

1.4.2 Homelessness

Homelessness has also been identified as a factor that can increase the risk of HCV infection amongst IDUs. Craine and Lyons (2006) describe the results of the blood-borne virus survey conducted in South Wales during 2004-2006. IDUs were opportunistically recruited to the survey from treatment services, needle exchange services and through community recruitment. From the 700 unique participants who were interviewed and gave dried blood spot samples at baseline, 287 (41%) tested HCV antibody negative at baseline and were successfully followed up for one year. During follow-up 17 seroconversions were observed amongst the 287 IDUs who were seronegative at baseline from which 12 of the 17 individuals who seroconverted (70%) had been homeless at some point during the follow-up period. The incidence of HCV infection among those who had been homeless during follow-up was calculated and compared to the corresponding incidence for those who have not been homeless. The results suggest that the HCV incidence rate ratio for IDUs who have been homeless is four times greater than those who have not been homeless (incidence for homeless: 12.4 per 100 person years; incidence for not homeless: 3 per 100 person years). Similarly, Hickman *et al.* (2007) found that the odds of being HCV positive were 3.1 times greater for IDUs who had reported recent homelessness (95% CI 2.1-4.5).

1.4.3 Incarceration

Imprisonment is another risk factor that can increase the risk of HCV infection amongst IDUs. Hickman *et al.* (2007) reported on a community recruited interview study of 1,058 IDUs in seven cities in England during 2004. Dried blood spot samples were tested for HCV antibodies and the results indicated that the odds of testing HCV positive were greater for those IDUs who had reported a period of incarceration than those who did not (odds ratio 2.2, 95% CI 1.7-3). Similar results were reported by Judd *et al.* (2005), where the odds of testing HCV positive were greater for IDUs who reported a period of incarceration (odds ratio 2.26, 95% CI 1.58-3.23).

1.5 Worldwide prevalence of HCV among IDUs

The prevalence of HCV is determined by the detection of HCV antibodies in either serum or saliva samples by enzyme-linked immunosorbent assays (ELISA).

Aceijas and Rhodes (2007) reviewed the grey and published literature released between 1998 and 2005 in order to examine the worldwide prevalence of HCV amongst IDUs. More recently, Nelson *et al.* (2011) performed a similar review of grey literature, conference abstracts, online resources and peer-reviewed databases to examine the global epidemiology of HCV and hepatitis B virus (HBV) infection in IDUs. Aceijas and Rhodes (2007) found data on HCV prevalence among IDU populations from 57 countries, while Nelson *et al.* (2011) found HCV prevalence data from 77 countries where there were IDU populations. Table 1.1 summarises the results from these reviews by region. From this table we can see that although prevalence amongst IDUs is high, there is wide variation in the rates reported, even within the same regions. Differences in the way that studies recruit IDUs and report the prevalence of HCV infection may account for some of the observed variation. Particularly, variations in study design can influence the characteristics of IDUs recruited and may also affect the estimates of HCV prevalence. A selection of the results are discussed below.

Region	HCV prevalence amongst IDUs (%)
Eastern Europe and Central Asia	10-96
South and South East Asia	4-99
East Asia and Pacific	34-93
North Africa and Middle East	2-100
Latin America and Caribbean	8-95
United States and Canada	8-90
Australia and New Zealand	25-88
Western Europe	2-93

Table 1.1: Summary of worldwide HCV prevalence amongst IDUs by region. Table is a summary of Table 2 presented in Aceijas and Rhodes (2007) and Tables 1, 2 and 3 presented in Nelson *et al.* (2011).

1.5.1 Eastern Europe and Central Asia

Both reviews found that Hungary and Slovenia were the only two countries in this region from which the reported prevalence was consistently below 50%. Russia, which contains the largest IDU population in this region (estimates suggest there are between 1,500,000 and 6,000,000 IDUs in Russia (EMCDDA 2010)), contained the highest estimates for HCV prevalence amongst IDUs (95% reported in Aceijas and Rhodes (2007) and 96% in Nelson *et al.* (2011)). In the Aceijas and Rhodes (2007) review, the high estimates of HCV prevalence came from major Russian cities. In St. Petersburg seven out of eight prevalence estimates were between 78% and 95% and in Moscow 11 out of the 12 HCV prevalence estimates were between 56% and 74% (Rhodes *et al.* 2006).

1.5.2 South and South East Asia

Both the lowest and highest HCV prevalence estimates for this region were found in Northern Thailand which had an IDU population of approximately 48,000 IDUs. The highest estimate for HCV prevalence was found in the capital city Bangkok. Evidence suggesting that HCV prevalence could be greater than 90% was found in countries with much larger IDU populations. For example, India, with an IDU population of approximately 1,163,000, had a national HCV prevalence estimate of 92% (Aceijas and Rhodes 2007).

1.5.3 East Asia and Pacific

Here, HCV prevalence estimates ranged from 33.5% to 99.3% with both the highest and lowest estimate coming from studies of HCV prevalence amongst IDUs in China (Aceijas and Rhodes 2007).

1.5.4 North Africa and the Middle East

Prevalence estimates from Israel, Syria and Lebanon were between 5% and 60.5%. However, these countries had relatively small IDU populations, less than 9,500 IDUs and the estimates were obtained from studies containing no more than 50 IDUs (Othman and Monem 2002; Ramia *et al.* 2003).

1.5.5 Latin America and the Caribbean

While the national estimate for HCV prevalence in Brazil was found to be between 39.5% and 69.7%, an estimated 84% of IDUs in Sao Paolo (the largest city in Brazil) were HCV antibody positive (Segurado *et al.* 2004). The lowest estimate (1.7%) was obtained from an area in Columbia where IDUs had been injecting for less than five years. There were only two settings in Mexico which had HCV prevalence data, both of which estimated an HCV prevalence of 100% (Rodriguez *et al.* 2002).

1.5.6 United States and Canada

The lowest estimate for the United States was found in Baltimore where 8% of 183 IDUs were found to be HCV antibody positive. Other estimates of prevalence in the United States ranged from 28% to 88.3% (Samuel *et al.* 2001)

1.5.7 Australia and New Zealand

Aceijas and Rhodes (2007) found that the national estimate for HCV prevalence amongst Australian IDUs was between 40% and 60% while Nelson *et al.* (2011) found that the prevalence of HCV ranged from 41%-68% (estimates from Nelson *et al.* (2011) were obtained from data published in 1990-91 and 1991-95). However, a more recent study by Aitken *et al.* (2008) involving 374 IDUs recruited to a social networks study from three drug markets in Melbourne between 2005 and 2007 found that the prevalence of HCV amongst IDUs was higher than this national estimate: HCV prevalence amongst the 196 participants in the study who had two or more blood samples available for testing was 71%.

1.5.8 Western Europe

HCV prevalence estimates for Western Europe ranged from 0% in Slovenia, which had an IDU population of approximately 7,500 to 96.8% in Germany which had an IDU population of 200,950. Reported HCV prevalence estimates for the United Kingdom were between 1.9% to 64% (Aceijas and Rhodes 2007). It is not clear from the review article where these estimates came from or the sample sizes from which the estimates were obtained.

1.6 Prevalence of HCV amongst IDUs in Scotland

Figure 1.1 shows the results of a recent survey of 2,513 IDUs in Scotland during 2008-2009 (NESI 2010). The results from this survey show that there is a great deal of variation in the prevalence of HCV amongst IDUs in the various Scottish Health Boards.

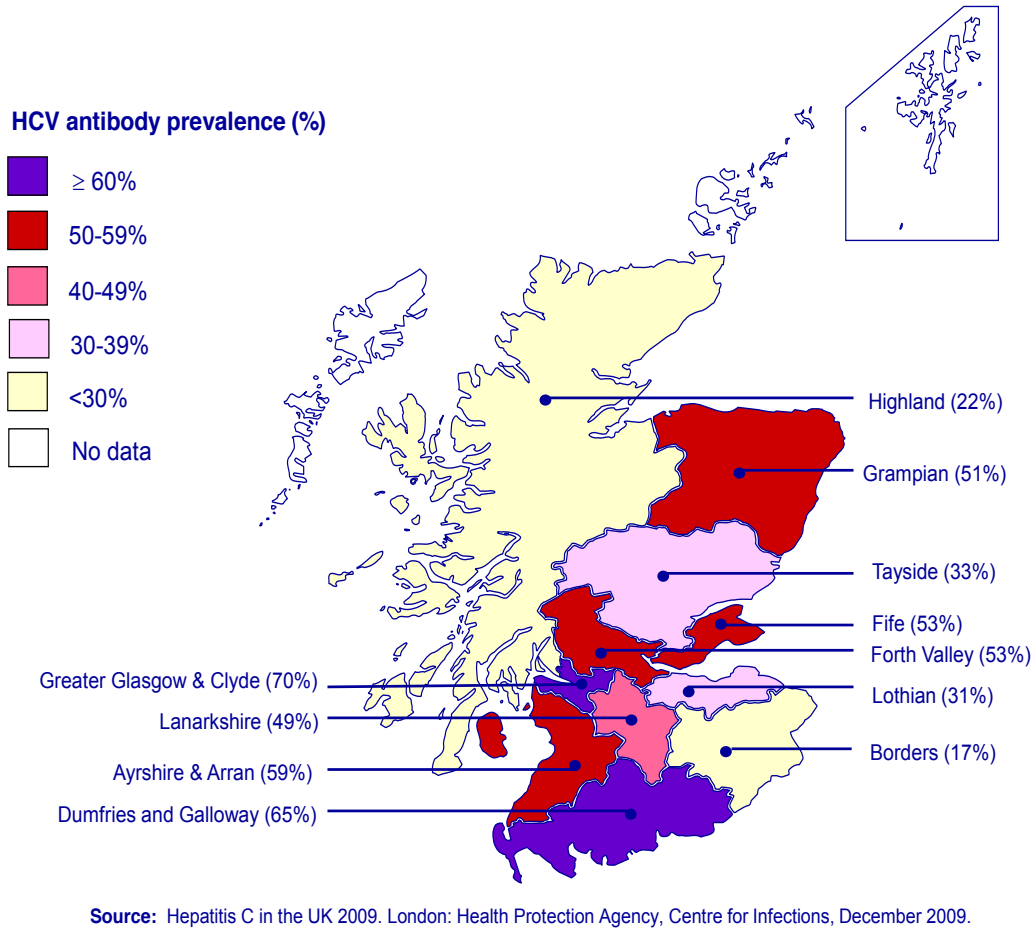

Figure 1.1: Prevalence of HCV (%) among 2,516 IDUs surveyed at needle exchange settings in Scotland during 2008-2009.

1.6.1 Prevalence of HCV amongst IDUs in Glasgow

Taylor *et al.* (2000) discuss the results of a survey of 1,949 IDUs from Glasgow who were recruited from in and out of treatment settings between 1990-1994 and 1996. The results suggested that HCV prevalence amongst Glasgow IDUs stood at 79% in 1990 and decreased to 66% in 1996. However, further reductions in HCV prevalence have not been observed (Hutchinson, Roy *et al.* 2006). A recent survey of 2,513 IDUs in Scotland during 2008-2009 (NESI 2010) found that Glasgow, which contains an estimated 37% (8,862/23,933) of the Scottish IDU population (Hay *et al.* 2009), had the highest HCV prevalence, estimated at 70%, 95% CI 67%-73%, (Figure 1.1).

Given the high prevalence of HCV amongst IDUs in Scotland, recent recommendations have focused on the prevention of HCV infection by improving intervention measures such as needle and syringe exchange programmes (Scottish Executive 2008b; Advisory Council on the Misuse of Drugs 2009). In the next section we shall describe these needle and syringe exchange programmes and their efficacy.

1.7 Needle and syringe exchange programmes

In 2004, the Scottish Government recognised that "Hepatitis C is one of the most serious and significant public health risks of our generation" (HPS 2007b). In recognition of this health issue, the Hepatitis C Action Plan was launched in September 2006. One of the main aims of the plan is to prevent the transmission of HCV amongst IDUs. The plan is a two phased one. Phase I, undertaken during September 2006-August 2008, involved gathering evidence to inform proposals for the development of HCV services during Phase II from 2008-2011 (Scottish Executive 2006).

Phase II comes with major Government investment: a total of £43 million will be invested during 2008-2011; and from this, £8 million will be distributed to NHS Health Boards for the development of prevention services (Scottish Executive 2008b).

Services providing needles and syringes to IDUs in Scotland have been developed since the late 1980s (Stimson and Donoghoe 1996; Goldberg *et al.* 1998).

Traditionally needles and syringe programmes (NSPs) only distributed needles and syringes, however, recent changes in legislation have allowed NSPs in the UK to distribute sterile drug preparation equipment such as citric acid, filters, swabs and cookers (ISD Scotland 2010; Gilles *et al.* 2010). To date there are 244 NSPs in Scotland which in 2008/09 distributed an estimated 4,123,568 needles and syringes and a range of drug preparation items (for example 145,872 filters, 320,149 spoons) to the Scottish IDU population (ISD Scotland 2010).

While there is evidence to indicate that these services have had a beneficial outcome on injecting risk behaviour and the transmission of HIV (Stimson and Donoghoe 1996; Judd *et al.* 1997; Limburg 2004) the incidence and prevalence of HCV (a more infectious virus than HIV) among IDUs remains high (Hutchinson *et al.* 2002). As a result, recent guidelines for the provision of injecting equipment have recommended an increase in the provision of injecting equipment across Scotland so that every injector has access to a sterile set of injecting equipment for every injection (Scottish Executive 2010). These recommendations have resulted in further legislative changes which have removed the limits on the number of needles and syringes that can be distributed to IDUs at any one time. However, the resources required to meet the guidelines are likely to be substantial since the shortfall in the number of needles and syringes distributed in Scotland is estimated to be several million per year (Scottish Executive 2010).

1.8 Opioid substitution therapy (OST)

OST is a process whereby opiate-dependent injectors replace their illegal drug with a prescribed dose of an oral opioid such as methadone. This daily prescription is usually taken in a supervised setting such as a pharmacy (Hutchinson *et al.* 2000). OST has been shown to be effective at reducing injecting drug use and therefore preventing blood-borne virus transmission. Hutchinson *et al.* (2000) conducted a one year cohort study of IDUs who were being treated with OST in Glasgow during 1996. The results of this study found that OST was associated with a large reduction in self-reported injection frequency and needle and syringe sharing rates. Of the 108 IDUs followed up, 78% reported that they injected daily at baseline. This fell to 2% after six months of continuous OST. Similarly, the sharing of needles and syringes in the month prior to interview fell from 28% to

2% after six months of continuous OST.

A more recent study involving a pooled analysis of 919 IDUs surveyed from six UK sites during 2001-09 examined the effects of OST and NSP on new HCV infection (Turner *et al.* 2011). The pooled analysis of the studies found that IDUs who were receiving OST had a 64% reduction in the odds of new HCV infection (odds ratio 0.36, 95% CI 0.19-0.70) compared to those who were not receiving OST. In addition, the analysis showed that, when compared to minimal harm reduction measures (<100% NSP and no OST), the combined effect of a high NSP coverage (defined as $\geq$100% versus $<$ 100% needles per injection) and OST resulted in an 80% reduction in the odds of new HCV infection (odds ratio 0.19, 95% CI 0.08-0.47). After adjusting for gender, homelessness and injecting crack cocaine, the authors found that the odds of new HCV infection were 0.41 (95% CI 0.21-0.82) for those on OST and 0.21 (95% CI 0.08-0.52) for those with a high NSP combined with OST. These results highlight the importance of OST and NSP in preventing the transmission of HCV amongst IDUs.

We have now completed our discussions on the biology and epidemiology of HCV infection. We now focus on the mathematical modelling of infectious diseases. We begin by discussing some of the key concepts and techniques involved in the modelling of infectious disease before discussing some infectious disease modelling work which highlights some of the valuable insights that can be gained from infectious disease modelling. We then give a brief overview of work that has modelled the spread of HIV and HCV amongst IDUs.

1.9 The mathematical modelling of infectious diseases

The history of mankind contains many examples of how infectious diseases in humans have had a major impact on civilisation. In the 14th Century bubonic plague, commonly known as the black death, swept through Europe reducing the European population by an estimated 30-60% (Alchon 2003). While the 20th Century saw the eradication of some infectious diseases, the morbidity and mortality associated with pandemic flu, HIV and other infectious diseases continue to leave their marks on mankind.

Given the importance of infectious diseases and their effects on the global population, it is not surprising that people have tried to understand how they are transmitted, controlled and prevented. Infectious diseases in humans are complex phenomena resulting in research that is both difficult, in terms of the moral and ethical issues surrounding research as well as the interactions between host and virus, and expensive, in terms of the resources needed to study complex phenomena. Mathematical and statistical models provide a simplified representation of this problem allowing for a more cost-effective research method, free from most of the ethical and moral issues that surround conventional research. For this reason, infectious disease models are increasingly being used by health organisations worldwide to understand the mechanisms necessary for disease spread, estimate the future burden of disease and determine the optimal control strategies for diseases such as HIV, HCV and pandemic influenza.

According to Vynnycky and White (2010), three kinds of model have been used to study infectious diseases: animal models, mechanical models and mathematical models. In animal models mice or chimpanzees are infected with the disease in question. Mechanical models were developed during the 1930s and provided the first techniques for stochastic simulation of infectious diseases, while mathematical models use symbols and algebraic formulae to describe the population parameters and the spread of the disease. Mechanical models originally consisted of a number of different coloured balls which were laid into containers, however, with the introduction of computers and computer simulation packages these methods are an important technique in the study of infectious diseases.

1.9.1 Model classification

There are a number of model classifications that can be used, dependent on the level of detail needed. Compartmental models divide the population up into categories (e.g. susceptible, immune) and track the spread of infection for each of the compartments. Individual based models track the spread of infection for every individual in the population and allows chance to determine whether or not each individual becomes infected. Network models explicitly model the contacts between individuals. In these models the risk of infection is dependent on the contacts of a particular individual. Such models are ideal for modelling the spread

of sexually transmitted diseases, ebola and tuberculosis.

1.9.2 Model structure

The choice of model structure depends on the natural course of infection, the required accuracy of model estimates, the data available and the characteristics of the study population (Keeling and Rohani 2008; Vynnycky and White 2010). Although models can vary in their complexity there are a number of common structures that can be used for modelling infectious diseases (see Figure 1.2).

Susceptible-Infectious (SI) models can be used to model the natural history of diseases such as HIV where the host remains infected and infectious for life. In these models a typical individual starts off susceptible, at some stage catches the disease and then remains permanently infected. Susceptible-Infectious-Susceptible (SIS) models can be used to describe curable diseases or diseases from which the host is susceptible to infection after treatment or recovery (Keeling and Rohani 2008). In these models a typical individual starts off susceptible, at some stage catches the disease, and after a short infectious period becomes susceptible again. Sexually transmitted diseases such as gonorrhea can modelled in this way. Susceptible-Infectious-Recovered (SIR) and Susceptible-Exposed-Infectious-Recovered (SEIR) models can be used to model infectious diseases where individuals can become immune to infection following treatment or recovery. An SIR model is similar to an SIS model except that at the end of his or her infectious period an individual enters the permanently removed class. An SEIR model is similar to an SIR model except that there is an exposed or incubating stage between the susceptible and infected stages. Many childhood diseases such as measles, rubella and chickenpox can be modelled using SEIR models. Susceptible-Infectious-Recovered-Susceptible (SIRS) models can be used to model diseases where individuals who have recovered from infection can be infected again (e.g. influenza). An SIRS model is similar to the SIR model except that this time the immunity is only temporary and at the end of the immune period the individual returns to the susceptible class.

Within this framework, models can be either deterministic or stochastic. Deterministic models use either difference or differential equations to describe what happens in a population over time. Difference equations describe the movement

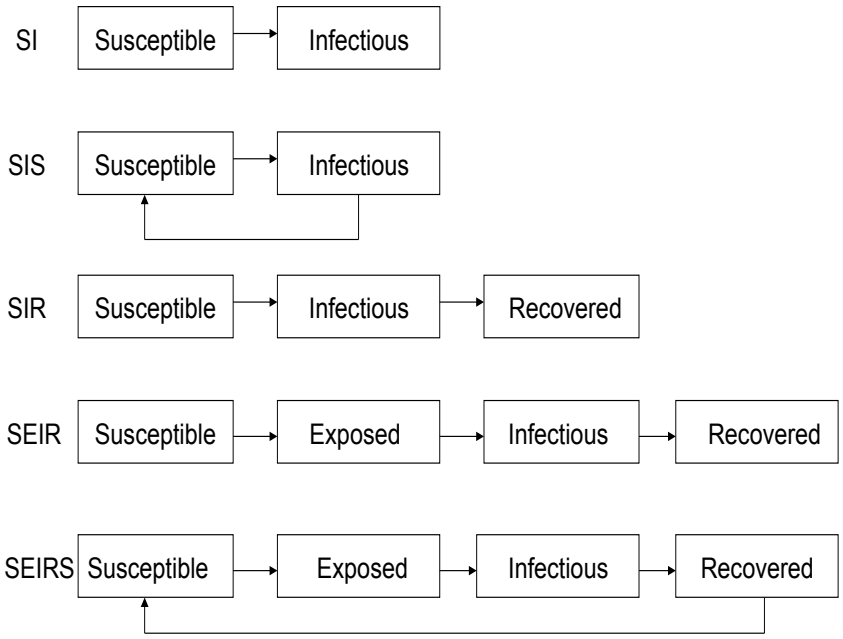

Figure 1.2: Common structures used for the modelling of infectious diseases. The arrows indicate the transitions for individuals within the population. Adapted from Vynnycky and White (2010).

of individuals between infectious classes using discrete time steps. The reliability of difference equations depends on the size of the time step used. If a large time step is used the epidemic curve becomes less smooth and this can result in an over-estimation or under-estimation at the next time step (Vynnycky and White 2010). One way to avoid this is to use differential equations, which use the rate of change to describe events that occur continuously in time. Stochastic models allow chance to decide on the infectious state of an individual. One way to allow chance to determine the infectious state of an individual is to draw a random number and specify the range that this number should lie if an infection has to occur. For example if the risk of infection is 40% then we could draw a random

number between zero and one and specify that this number must lie between 0 and 0.4 for disease transmission to occur. If the number drawn is outside our specified range then the individual remains susceptible.

1.9.3 Examples of infectious disease modelling work

No matter which method is used, infectious disease models can provide valuable insights into how infectious diseases spread and are controlled.

The Kermack and McKendrick model

Kermack and McKendrick (1927) developed a mathematical model in order to determine whether the termination of an epidemic occurs only when there are no susceptible individuals left in the population or whether the effects of infectivity, recovery and mortality result in this termination occurring while there are a number of susceptible individuals left in the population. The model used a system of non-linear differential equations to describe the rate of change of the number of susceptible (x), infectious (y) and recovered (z) individuals in a population who are all equally susceptible to the disease and where a single infection confers immunity to infection. The system of equations which governed the behaviour of the model can be written as follows:

$$\begin{aligned}
\frac{dx}{dt} &= -\beta xy, \\
\frac{dy}{dt} &= \beta xy - \gamma y, \\
\frac{dz}{dt} &= \gamma y,
\end{aligned}$$

where β is the rate of infection and γ is the rate at which individuals recover from their infection and become immune.

One of the most important results contained in this work is the Threshold Theorem which showed that an epidemic does not necessarily terminate when there are no susceptible individuals left in the community. The theorem showed that the emergence of an epidemic is dependent on a population density threshold. If an infection was introduced into a community where the population density was less than or equal to this threshold value there would be no epidemic. In

contrast, if the population density was greater than the threshold density when infection was introduced then an epidemic would occur. Furthermore, the authors found that the size of the epidemic depended on how much bigger than the threshold density the initial population density was. If the population density was only slightly larger than the threshold density a small epidemic would occur. Likewise, if the population density greatly exceeded the threshold density then a large epidemic would occur.

The book of N. T. J. Bailey

The ever expanding field of mathematical modelling of infectious diseases in the 20th century resulted in a large number of mathematical references to the population theory of infectious diseases which were widely scattered throughout the literature (Bailey 1975). The book of N. T. J. Bailey (Bailey 1975) titled "The mathematical theory of infectious diseases and its applications" is the second edition of a book published by Bailey in 1957 (Bailey 1957) in which the author attempts to bring all the interesting results together into a single text which gives a systematic treatment of the field. The book is aimed at increasing the understanding of the mathematical and statistical techniques that are used to gain insights into the mechanisms behind infectious disease spread. It contains information on a large number of mathematical modelling techniques, ranging from simple deterministic models to more complicated spatial and chain-binomial models, and describes how these techniques can be used to model different disease epidemics. In addition to all the technical detail, the book discusses how the techniques described in the book can influence vaccination strategies and public health control.

The work of Hethcote on communicable disease models

Hethcote (1976) considered infectious disease models where the spread of disease is governed by two dimensional non-linear systems of ordinary differential equations. In this modelling work, Hethcote assumed that the infection occurs in a homogeneously mixing population of size N, where N is both large and constant. If the model incorporated births and deaths, he assumed that they occurred at the same rate. Hethcote examined several deterministic models which incorporated

various different biological and demographic factors. For all of these models the author proved theorems which describe the asymptotic behaviour of the models and show how different model structures result in different kinds of epidemic. One of the models considered is an SIRS model which allows individuals who recover from infection to gain temporary immunity. This kind of model structure is suitable for modelling influenza, smallpox, cholera and tetanus (Hethcote 1976). The system of equations which governed the behaviour of this SIRS model are as follows:

$$\begin{aligned}\frac{dS(t)}{dt} &= -\lambda IS + \delta - \delta S + \alpha R,\\ \frac{dI(t)}{dt} &= \lambda IS - \gamma I - \delta I,\\ R(t) &= 1 - S(t) - I(t),\end{aligned}$$

where the daily contact rate λ is the average number of contacts per infective per day, γ is the daily recovery removal rate per infective, δ is the daily death removal rate per individual and α is the daily rate at which individuals lose their immunity to infection. Here S denotes the fraction of the total population that are in the susceptible class at time t, I denotes the fraction of the total population that are in the infected class at time t and R denotes the fraction of the population that are in the recovered class at time t.

The author proved that the value of the infectious contact number determined the long term behaviour of the model. He showed that provided that the disease was initially present when the infectious contact number exceeds one, the fraction of susceptible and infectious individuals in the population tends to an endemic equilibrium value. If the infectious contact number is less than one, the number of infectious individuals will decrease until the system reaches the DFE.

The Reed-Frost model

The Reed-Frost model describes a fast spreading infection in a closed population. The model assumptions are as follows (Frost 1976; Fine 1977):

1. Infection is spread directly from infected individuals to others by a certain type of contact and in no other way.

2. After such a contact in a given time period, any susceptible individual in the population will develop the infection and will be infectious to others in the next time period.

3. After this period of infectivity, the infectious individual is wholly immune.

4. Each individual has the same fixed probability of coming into adequate contact with any other individual in the group within one time period.

5. The above conditions remain constant for the whole epidemic.

In mathematical terms the deterministic model can be written as follows:

$$S_{t+1} = S_t - C_{t+1}, \tag{1.1}$$

$$C_{t+1} = (1 - q^{C_t})S_t, \tag{1.2}$$

where S_t and C_t respectively denote the number of susceptibles and cases at time step t, S_{t+1} and C_{t+1} respectively denote the number of susceptibles and cases at the next time step and $(1 - q^{C_t})$ denotes the probability that a susceptible individual has an effective contact with at least one case at time t. Note that q^{C_t} denotes the probability that a susceptible individual does not have an effective contact with any cases at time t. Equation (1.1) allows us to determine the expected number of susceptibles at the next time step while equation (1.2) allows us to determine the expected number of cases at the next time step.

Since the model assumes that susceptibles make infected contacts independently of each other and that every susceptible has the same probability of being infected through an effective contact with infectives, it is possible to introduce the binomial distribution into this model (Becker 1981). This allows us to write a stochastic version of the Reed-Frost model where the probability of a specified prevalence in a subsequent time step is given by a standard binomial expression (Bailey 1957; Fine 1977). According to Fine (1977) the process of converting the deterministic formulation of the Reed-Frost model to the stochastic formulation is easily illustrated by comparing the epidemic process in this model to a series of binomial trials. At each stage of the epidemic, the probability that a susceptible individual will become infected is given by $(1 - q^{C_t})$. Hence, the events at each stage of the infection can be thought of as tossing S_t coins that each have a prob-

ability of $(1 - q^{C_t})$ of landing cases up. Therefore, the probability that exactly x susceptibles will be infected at a particular stage of the epidemic is given by

$$P(C_{t+1} = x | S_t = s_t) = \frac{s_t!}{x!(s_t - x)!}(1 - q^{c_t})^x (q^{c_t})^{s_t - x}, \text{ for } x = 0, 1, 2, ..., s_t.$$

This equation describes the probability of a specific disease prevalence in the community at time step t, given the values of S_t and C_t at time step t.

The stochastic Reed-Frost model can be represented by a simple mechanical model (Fine 1977). Balls of four separate colours are needed: one colour for those susceptible to infection, one for those who are immune, one for those who are infectious and one to act as contact blockers. A number of balls equal to the number of individuals of each stage of infection at time t are placed into a container along with a number of contact blockers. These balls are then randomised and poured into a trough in single file. All coloured balls not separated by a contact blocker have an effective contact and hence the spread of infection can be recorded (e.g. a susceptible ball next to an infected ball means that the susceptible ball becomes infected). The population of balls is altered to represent the new account for the spread of infection and the process is repeated until either there are no susceptible or no infected individuals left in the population. While computer simulations are now used to perform this kind of operation, this mechanical representation of the Reed-Frost model serves as an interesting example of the role of chance in an epidemic process.

The model of Meltzer *et al.*

Using the SIR model framework, Meltzer *et al.* (2001) created a Markov chain model, a model where the probability distribution of the next state is based entirely on the current state and not on the past states, to examine the most effective way to control an outbreak of smallpox which had been released into a susceptible population as part of a bio-weapon. The model describes four infectious classes: incubation (for those who have been infected but have no clinical symptoms), pre-eruptive (where patients become feverish), overtly symptomatic (where a rash or similar symptoms can be readily noted) and no longer infectious. The model assumes that there is an infinite supply of susceptible individuals in the population. From their numerical simulations, the authors found that:

1. Quarantine alone would be able to stop the spread of disease but only if a minimum of 50% of those with overt symptoms were quarantined daily. Furthermore, if the quarantine process was started 30 days after the release of the virus then there would be a maximum of 50 new cases per day, a total of 2,300 cases over the course of the epidemic and no further cases after day 240 of the epidemic. If the quarantine process did not start until day 45, then there would be a maximum 120 new cases per day, a cumulative total of 6,800 cases over the course of the epidemic. However, if the quarantine process was started 15 days earlier, then on day 15 of the epidemic, then there would only be a maximum of 20 new cases per day and a total of 1,750 cases over the course of the epidemic.

2. A vaccination programme, starting on day 30 of the epidemic, would need to reduce the average transmission rate of the virus to 0.85 persons per infected case in order for there to be no further cases by day 365 of the epidemic. If this was achieved there would be a total of approximately 2,857 cases of smallpox in the population.

3. It is possible to combine vaccination and quarantine measures to stop the spread of disease by day 365 of the epidemic. A quarantine strategy which removes 25% of the overtly symptomatic cases daily would need to be combined with a vaccination campaign which reduces the rate of transmission rate of the virus by 33% (from three persons per infectious case to two persons per infectious case) would eliminate the spread of disease by this date. However, the total number of smallpox cases would rise to 4,200 over the course of the epidemic which is much greater than the number of cases that would result from the quarantine only strategy.

Although the authors describe the total number of cases of smallpox occurring in the population, the stochastic nature of the model means that deterministic predictions cannot be made. Therefore, we interpret these totals to be median values from a number of simulations initialised with the same values. The results from this modelling work show how infectious disease models can be used to examine the potential of many different control measures and advise health organisations and policy makers on the best course of action during an epidemic. As well as being used to examine the impact of control measures on the spread

of disease, infectious disease models have also been used to understand the epidemiology of infectious diseases.

An influenza model

In early 1978 a boarding school in England, which housed 763 pupils, was the subject of an influenza outbreak which lasted two weeks. During the course of this epidemic a total of 512 pupils were confined to bed after reporting to the school infirmary with symptoms of influenza. Both Murray (1993) and Keeling and Rohani (2008) discuss the SIR model that was used to help understand the spread of this influenza virus. The model has the following governing equations

$$\frac{dS}{dt} = -rSI, \tag{1.3}$$

$$\frac{dI}{dt} = rSI - aI, \tag{1.4}$$

$$\frac{dR}{dt} = aI, \tag{1.5}$$

where r denotes the rate of infection of a single susceptible individual by a single infected individual and $1/a$ denotes the average infectious period. Equations (1.3), (1.4) and (1.5) describe how the number of susceptible, infected and recovered pupils respectively changes over time. Using a least squares algorithm, which obtains best fit parameter estimates by minimising the sum of squares of the differences between predicted and observed cases, the average infectious period $1/a$ during this epidemic was an estimated 2.2 days and the rate of infection was estimated as 0.00218 per day. This example shows how it is possible to use data on outbreaks combined with infectious disease models to estimate how aggressive a particular disease is and how long the symptoms associated with infection will last.

1.10 The basic reproductive number

The basic reproductive number, R_0, is an important concept in the modelling of infectious diseases. This dimensionless number can immediately tell us whether an infectious disease can persist in a population or if eventual disease elimination

will occur. It is formally defined as the expected number of secondary cases produced in a totally susceptible population by a typical infected individual during their entire period of infectiousness (Diekmann *et al.* 1990; Vynnycky and White 2010).

The condition $R_0 > 1$ is considered another important threshold in infectious disease modelling which, when satisfied, results in each infectious person spreading the infection to more than one person. This gives rise to an epidemic situation. If $R_0 < 1$, the infection does not fully replicate itself and thus the infection cannot grow. Thus if $R_0 < 1$ then it is reasonable to expect that the disease will die out and the system will tend to the DFE. Figure 1.3 illustrates the implications of an infectious disease with $R_0 = 2 > 1$ over three generations or time steps.

From Figure 1.3 we can see that for each successive time interval, there is a three-fold increase in the number of infectious individuals in the population. This results in an epidemic situation where the number of infectious individuals increases exponentially until the lack of susceptible individuals slows the process.

The actual values for R_0 depends largely on the disease in question and the circumstances surrounding the population at the time of the epidemic (for example hygiene conditions, health care provision and the existence of intervention measures to prevent infection). In order to highlight the possible variation in R_0 values we have tabulated the R_0 values, taken from Anderson and May (1991) and Vynnycky and White (2010), for a number of well known infectious diseases (Table 1.2).

Infection	R_0 estimate
Diphtheria	6-7
Influenza	2-4
Malaria	5-100
Measles	12-18
Mumps	7-14
Small Pox	5-7

Table 1.2: Basic reproductive numbers for several well known infectious diseases.

We have now finished discussing some of the background concepts for infectious disease modelling. We are interested in developing mathematical models

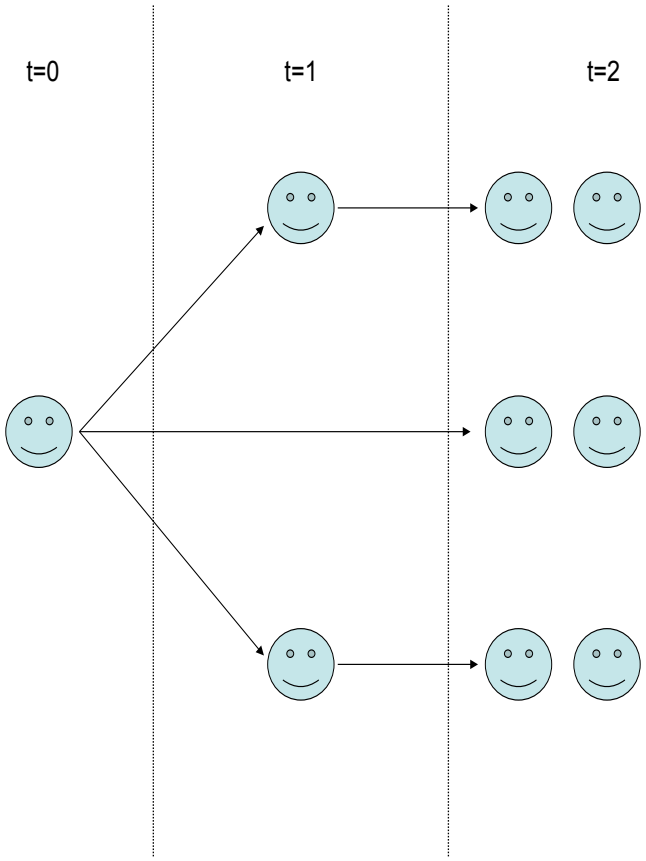

Figure 1.3: Graphic representation of the implications of an infectious disease with $R_0 = 2$. Figure has been adapted from Vynnycky and White (2010).

for the spread of HCV amongst IDUs. However, as we have already pointed out, there are many similarities between how HCV and HIV is spread amongst IDUs and whilst there is quite a bit of existing modelling work on how HIV spreads amongst IDUs there is less on how HCV spreads amongst IDUs. We now review some of the work that models the spread of HIV amongst IDUs. The techniques used to develop and analyse these models can be used to develop models for the spread of HCV amongst IDUs.

1.11 Mathematical modelling the spread of HIV amongst IDUs

Mathematical modelling techniques have been used extensively during the HIV epidemic among IDUs. They have helped understand the epidemiology of HIV infection amongst IDUs, the risk factors associated with infection, and have provided evidence to support the introduction, and subsequent development, of interventions (such as needle exchange programmes) as an effective way to combat the spread of HIV amongst IDUs.

1.11.1 The "needles that kill" model of Kaplan

Kaplan (1989) presented one of the first mathematical models developed explicitly for the spread of HIV and AIDS amongst IDUs through the sharing of needles and syringes in shooting galleries. This work provided useful insights into the transmission of HIV in shooting galleries and suggested the kind of data that was needed in order to better understand HIV transmission (e.g. needle and syringe sharing rates, the likelihood of needle and syringe cleaning and the mean duration of needle and syringe sharing risk behaviour). Furthermore, the model showed how effective intervention measures such as bleaching needles or distributing clean injecting equipment could be.

In order to model the fraction of the population infected with HIV at time t, denoted $\pi(t)$ in the model, the author made the following assumptions:

1. There are m shooting galleries (locations where IDUs rent the same needles and syringes) in existence and all injecting drug use takes place in shooting galleries. Furthermore, an IDU injects once per shooting gallery visit.

2. Each IDU randomly visits shooting galleries at a rate λ, independently of the actions of the other IDUs. Since IDUs only inject once per shooting gallery visit this assumption implies that, for all IDUs, λ is the per capita needle and syringe sharing rate.

3. All injecting equipment will become infectious after it is used by an infectious IDU. In addition, a needle and syringe that is used by an uninfectious IDU may be flushed (with probability θ) which will render it uninfectious

(i.e. the infectious contents of the needle and syringe are completely removed during the injecting process). This assumption means that although uninfectious IDUs are at risk of HIV infection after using infectious needles and syringes, they may also remove that risk for the IDU who next uses the needle and syringe.

4. The transmission probability of HIV through shared needles and syringes is α per injection. Furthermore, IDUs can become infected with HIV only through the sharing of needles and syringes. This assumption implies that there is no variability in the infectivity of HIV and that other known transmission routes such as sexual intercourse do not have an impact on the disease burden in this population.

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

By considering the number of infected IDUs in the population at time $t+\Delta t$ as well as the number of infected needles at time $t+\Delta t$, where Δt is a small increment in time, Kaplan derived the following differential equations which govern the spread of the disease:

$$\frac{d\pi(t)}{dt} = [1-\pi(t)]\lambda\beta(t)\alpha - \pi(t)\mu,$$
$$\frac{d\beta(t)}{dt} = \lambda\gamma\pi(t) - \lambda\gamma\beta(t)[1-[1-\pi(t)](1-\theta)].$$

Here $\beta(t)$ denotes the fraction of infected needles and syringes at time t, and γ denotes the gallery ratio or the number of IDUs per shooting gallery. In addition to these equations, the author derived an expression for the basic reproductive number, R_0, which is given by $\lambda\alpha/\mu\theta$ and showed that this expression must exceed one for an endemic equilibrium solution to exist.

In his first set of numerical simulation results, Kaplan examined the effect that different gallery ratios have on the spread of HIV in this population. The results showed that for large values of γ, the spread of HIV amongst this IDU

population reaches equilibrium very quickly, whereas low values of γ result in a much slower initial disease spread.

Kaplan then introduced heterogeneity in needle and syringe sharing rates into the model and examined the effects that this heterogeneity has on the model results. Numerical simulations found that IDUs with more active needle and syringe sharing behaviour are infected more quickly with HIV than those with more moderate levels of needle and syringe sharing.

The model is then adapted further in order to allow for the cleaning of needles and syringes. Here the author assumes that every IDU, infected or not, cleans their needle and syringe after use with probability ξ and that this cleaning is effective in clearing the viral load from the needle and syringe. The modelling results showed that the cleaning of needles and syringes can have an impact on the prevalence of HIV in the population and can even eliminate HIV, even if the cleaning process is not perfect, or if IDUs do not always clean their needles and syringes.

While the work contained in Kaplan (1989) highlighted important risk factors for HIV infection and the potential benefits of needle and syringe cleaning practices, later work undertaken by Kaplan and O'Keefe (1993) focused on, what was then, a novel experiment in the prevention of HIV infection amongst IDUs.

1.11.2 The "let the needles do the talking" model of Kaplan and O'Keefe

In November 1990, New Haven, Connecticut, USA implemented a pilot needle and syringe exchange program to combat the spread of HIV and AIDS amongst its IDU population. In order to evaluate the effectiveness of the program, a unique syringe tracking and testing system (STT) was implemented. A unique tracking number was assigned to each needle and syringe distributed by the program. As a consequence of this tracking number the program was able to record the program ID for the recipient, the date that the needle and syringe was distributed, the date that the needle and syringe was returned, the program ID of the person returning the needle and syringe, and the location of the syringe distribution and return centre. In the event that a returned needle and syringe was not initially distributed by the project, the project ID of the person returning the needle

and syringe and the date and location that the return took place was recorded. Samples of the returned needles and syringes were then tested for HIV proviral DNA.

Kaplan and O'Keefe (1993) developed a mathematical model to evaluate the effectiveness of the New Haven needle exchange program. The STT system developed to help determine the effectiveness of the program provided researchers with some shocking and some interesting results. At the beginning of the program a total of 44 of the 48 needles and syringes obtained from a local shooting gallery (91.7%) and 108 out of 160 street needles (67.5%) tested positive for HIV. Although the prevalence of HIV amongst street needles was lower than the prevalence of HIV amongst the shooting gallery needles these figures represented a severe risk of HIV infection amongst IDUs. More encouraging results were obtained as the program progressed. By the middle of March 1991, a total of 579 needles and syringes had been tested for HIV. A total of 291 (50.3%) of these 579 needles and syringes tested positive for HIV infection. Moreover, an additional 367 needles and syringes were tested after March 1991 and the prevalence of HIV infection amongst these needles was found to be 40.5% (107/367).

In order to link these encouraging results on the operation of the program to the changes in the rate of new HIV infection, Kaplan and O'Keefe (1993) developed a mathematical model for the spread of HIV infection amongst IDUs through the sharing of needles and syringes. Data obtained from the STT and surveys of IDUs attending the program were used to parameterise the model.

The model governing equations are:

$$\begin{aligned}
\frac{d\pi(t)}{dt} &= \lambda[1-\pi(t)](1-\phi)\beta(t)\alpha - \pi(t)\mu, \\
\frac{d\beta(t)}{dt} &= [1-\beta(t)]\lambda\gamma\pi(t) - \beta(t)[\rho + \lambda\gamma\theta(1-\pi(t))], \\
C(\tau) &= \int_0^\tau [1-\pi(t)]\lambda(1-\phi)\beta(t)\alpha dt.
\end{aligned}$$

Here λ denotes the needle and syringe sharing rate, ϕ denotes the probability of cleaning a needle prior to injection, μ denotes the rate at which an HIV infected IDU leaves the population, α denotes the per injection transmission probability of HIV infection, ρ denotes the needle exchange rate, γ denotes the ratio of program clients to needles in circulation, $\pi(t)$ denotes the prevalence of HIV

infection amongst program clients and $\beta(t)$ denotes the fraction of needles that are infected with HIV. The first equation states that an uninfected IDU becomes infected with probability α after sharing needles and syringes that have not been cleaned prior to use. Furthermore, infected IDUs leave the sharing, injecting population at a per capita rate μ per year. The second equation states that clean needles and syringes become infected after they have been used by an HIV infected IDU. Infected needles and syringes are rendered uninfectious if they have been cleaned prior to use of if they have been exchanged. The third equation calculates the cumulative incidence of HIV infection per IDU during the time interval $(0, \tau)$. Note that $\tau = 0$ indicates the beginning of the needle exchange program.

After estimating the necessary parameters the authors conducted a conservative analysis by comparing the incidence of HIV infection without needle exchange services to the incidence of HIV with needle exchange rate of $\rho = 0.25$ per year obtained from STT data from November 1990-February 1991. The model results suggested that the introduction of needle exchange services resulted in a decrease in HIV incidence. In the absence of needle exchange services HIV incidence was estimated at 6.4 infections per 100 person years while the incidence of HIV infection post needle exchange introduction was estimated at 4.3 infections per 100 person years. Therefore, the model results implied that there had been a 33% reduction of HIV incidence since the needle exchange program was introduced.

Further analysis of the STT data found some other important results. Firstly, there was no increase in the frequency of injecting drug use as a result of the program and secondly one in six IDUs who joined the program had entered a drug treatment program. Before this work needle exchanges were not common. There was opposition to needle exchanges as some people felt that they would encourage injecting drug use. Indeed, Connecticut legislation at the time did not allow needle exchanges to operate within the law. There was doubt about whether needle exchanges would effectively prevent HIV transmission amongst IDUs. The paper of Kaplan and O'Keefe, done in collaboration with public health workers conclusively proved that needle exchanges could slow the transmission of HIV.

1.11.3 The model of Greenhalgh and Hay (1997)

Greenhalgh and Hay (1997) adapted the Kaplan (1989) model to incorporate more realistic assumptions relating to the spread of HIV among IDUs. These assumptions involved:

(i) changes to allow HIV diagnosed and undiagnosed IDUs to visit shooting galleries at different rates (previously assumed the same),

(ii) introducing different transmission probabilities for flushed and unflushed needles (in the model of Greenhalgh and Hay it is possible for an infectious needle used once by a susceptible IDU to be flushed; in other words cleared of infectious blood during the injection process, thus ending up uninfectious), and

(iii) changes to allow for the possibility that HIV infected IDUs may not always leave a needle infected before cleaning.

The authors performed an extensive mathematical and numerical analysis of their model and found that the model behaviour was governed by R_0. They were able to show that when $R_0 < 1$ their system would reach the DFE. If $R_0 > 1$, they showed that there was a unique positive endemic equilibrium which was locally stable.

1.11.4 The model of Lewis and Greenhalgh (1999)

Lewis and Greenhalgh (1999) derived a deterministic model for the spread of HIV amongst IDUs in order to examine the possibility of using HIV testing as an effective control strategy against the spread of AIDS in the IDU population. This model is based on the work of Kaplan (1989), Kaplan and O'Keefe (1993) and Greenhalgh and Hay (1997). The IDU population is separated into two groups: those who have not been tested for HIV (type one IDUs) and those who have been tested for HIV (type two IDUs). The model keeps track of the fraction of type one IDUs who are infected with HIV at time t, denoted by $\pi_1(t)$, the fraction of type two IDUs who are infected with HIV at time t, denoted by $\pi_2(t)$, and the fraction of needles and syringes that are infected with HIV at time t, denoted by $\beta(t)$.

The authors perform an extensive mathematical analysis of the model and use numerical simulations to verify their analytical results. Similarly to Kaplan (1989) and Greenhalgh and Hay (1997) the authors found that the system would tend to an endemic equilibrium only if $R_0 > 1$. Further simulations suggested that HIV testing could be an effective control strategy against the spread of AIDS but only if IDUs were regularly tested and once they were aware that they were infected with HIV they reduced their needle and syringe sharing significantly.

1.11.5 The model of Greenhalgh and Lewis (2000)

Greenhalgh and Lewis (2000) extended the Kaplan and O'Keefe (1993) model to incorporate three stages of variable infectivity prior to the onset of AIDS. This involved separating the class of infectious IDUs and needles into three according to the different levels of infectivity, thus allowing IDUs to progress through three infectious classes before the onset of AIDS as well as allowing needles and syringes to exist in three infectious classes. In this work the authors assumed that the infectivity of a needle and syringe was determined by the infectivity of the IDU who last used the needle and syringe. This assumption resulted in model predictions that were optimistic compared to other possible assumptions and provided lower bounds on the fraction of IDUs and needles infected with HIV.

Greenhalgh and Lewis conducted a mathematical and numerical analysis of their model and found that their model behaviour was also governed by R_0. Their analysis, which was confirmed by numerical simulations, found that when $R_0 \leq 1$ the system reached a DFE and when $R_0 > 1$, and HIV is initially present in the population (in either IDUs or needles), the system will tend to a unique locally stable endemic equilibrium. Numerical simulations compared the Kaplan and O'Keefe (1993) model to their three stage infectivity model. The results of these simulations showed that both models reached an endemic equilibrium after approximately 50 years and that the three stage infectivity model had a lower long term HIV prevalence than the corresponding model of Kaplan and O'Keefe (1993).

1.11.6 The model of Lewis and Greenhalgh (2000)

Lewis and Greenhalgh (2000) also extended the Kaplan and O'Keefe (1993) model to incorporate three stages of variable infectivity prior to the onset of AIDS. In contrast to the work in Greenhalgh and Lewis (2000), the authors assumed that the infectivity of a needle and syringe was determined by the most infectious IDU who last used the needle and syringe. This means that needles and syringes become progressively more infectious until they end up in the highest infectivity stage. This assumption resulted in model predictions that were pessimistic and provided upper bounds on the prevalence of HIV amongst IDUs and needles. The mathematical analysis performed by the authors found similar results to those obtained by Greenhalgh and Lewis (2000). Numerical simulations were used to compare the HIV prevalence obtained from this model to that obtained from the Kaplan and O'Keefe (1993) model. The results of these simulations found that both models reached an endemic equilibrium solution with the three stage infectivity model reaching equilibrium sooner than the Kaplan and O'Keefe (1993) model. Furthermore, the three stage infectivity model had higher long term HIV prevalence estimates than the Kaplan and O'Keefe (1993) model.

1.12 Modelling the transmission of HCV infection among IDUs

In this section we review models, which approximate the spread of HCV amongst IDUs through the sharing of needles and syringes. A literature search of PUBMED (January 1966 to July 2009), EMBASE (January 1980 to July 2009) and Web of Knowledge (January 1987 to July 2009) was performed to identify English language, peer reviewed articles on the dynamic modelling of the transmission of HCV amongst IDUs. The following search terms were used:

1. Hepatitis C or HCV;
2. model$;
3. inject$ or IDU$ or injecting drug use$ or injection drug use$ or injector$ or intravenous drug use$;

4. transmission;

5. (1) and (2) and (3) and (4);

where the $ symbol allows terms to be truncated thus giving all variant spellings or endings from the symbol onwards.

The above search identified a total of 89 papers. Closer examination of the abstracts and articles identified a total of four papers which had dynamically modelled the transmission of HCV amongst IDUs through the sharing of needles and syringes; these studies focused on IDU populations in Australia (Murray *et al.* 2003), Glasgow (Hutchinson, Bird *et al.* 2006), London (Vickerman *et al.* 2007) and Pakistan (Vickerman *et al.* 2009).

The following subsections describe the approaches used in each of these articles as well as the results obtained. The key points are summarised in Table 1.3.

1.12.1 Models that examine the spread of HCV and HIV amongst IDUs

In this section we shall discuss some models that examine the spread of HCV and HIV amongst IDUs.

The model of Murray *et al.* (2003)

Murray *et al.* (2003) developed a mathematical model which used differential equations to simulate the spread of HCV and HIV amongst current IDUs in Australia to examine the potential impact of changes in needle and syringe sharing rates on the prevalence of HCV and HIV in this IDU population. The model keeps track of the number of current IDUs who have the infection of interest at time t, denoted $I(t)$. Here, new infections are assumed to occur through the sharing of injecting equipment and other routes (for example sexual transmission). The term sharing of injecting equipment refers to the sharing of needles and syringes, considered to be the dominant transmission route, as well as other injecting paraphernalia such as swabs and tourniquets. The rate of change of the number of IDUs infected with the disease of interest is given by the following

Reference	Model description	Research questions(s)
Murray *et al.* (2003)	Deterministic compartmental model for the spread of HCV (1960-2000) and HIV (1979-2000) amongst IDUs in Australia	Examine the potential impact of changes in sharing rates on the prevalence of HCV and HIV
Hutchinson, Bird *et al.* (2006)	Stochastic simulation model for the spread of HCV amongst IDUs in Glasgow during 1960-2000	Estimate incidence of HCV in Glasgow during 1960-2000 and determine the effectiveness of interventions during 1988-2000
Vickerman *et al.* (2007)	Deterministic compartmental model for the spread of HCV amongst IDUs in London	Explore the impact of intervention measures that reduce needle and syringe sharing
Vickerman *et al.* (2009)	Deterministic compartmental model for the spread of HCV and HIV in Pakistan	Project the future HCV/HIV epidemic and estimate the impact of a generic intervention on the prevalence of HCV/HIV

Reference	Summary of results	Validation of model results
Murray *et al.* (2003)	Under the then current level of sharing HCV prevalence would remain high and HIV prevalence would remain low	The model was validated by comparing the modelled incidences with estimates from scientific literature
Hutchinson, Bird *et al.* (2006)	Incidence (per 100 person-years) was 6-40 (1960-1976), 78-89 (1977-1986) and 18-30 (1990-2000); 4,500 infections prevented by interventions	Model simulations were compared to HCV community-wide surveys of Glasgow IDUs
Vickerman *et al.* (2007)	Interventions must reduce sharing amongst all IDUs and be sustained for at least 8 years for HCV prevalence to fall	The model was fitted to seroprevalence data from London during 2002-2003
Vickerman *et al.* (2009)	The prevalence of HCV/HIV is likely to increase if there is no change in risk behaviour. To have the greatest impact on HCV/HIV prevalence interventions must reach all IDUs	Model projections were checked against the prevalence of HCV amongst HIV-infected IDUs

Table 1.3: Summary of modelling work on the transmission of HCV infection amongst IDUs through the sharing of needles and syringes.

equation

$$\frac{dI(t)}{dt} = aI - bI + c,$$

where aI denotes the per year average rate of new infections from needle and syringe sharing, bI denotes the per year average removal rate of IDUs and c denotes the per year rate of new infections from non-needle and syringe sharing risk behaviour, that is through the sharing of drug preparation equipment and sexual transmission.

The model simulated the incidence and prevalence of HCV amongst Australian IDUs during 1960-2000 and HIV amongst Australian IDUs during 1979-2000 and was parameterised using data from these periods. Validation of the model results was achieved by comparing the modelled incidence of infection to incidence estimates from published literature sources. The authors then used the model to determine the critical level of needle and syringe sharing, denoted s_c, below which the number of infections would fall to a minimal level.

Results

For HIV the critical level of needle and syringe sharing was far greater than what was then the current estimate of needle and syringe sharing. The results suggested that the level of needle and syringe sharing would need to increase from its baseline parameter estimate of six sharing partners per year to 17 sharing partners per year, suggesting that under current behaviour HIV prevalence would remain low. For HCV, however, the critical level was half the current estimate of needle and syringe sharing, suggesting that HCV prevalence would remain high.

Limitations of this research

This modelling work shows how the HIV and HCV epidemics in Australia are very different epidemics and that intervention strategies used to control one epidemic may have a limited effect on the other. However, there are a number of limitations that must be considered here. Firstly, the model does not allow for the differences in the natural course of HIV and HCV infection and does not allow infection with one disease to affect the risk of infection with the other which may

influence the results. Secondly, the calculations for the critical levels of needle and syringe sharing assume that the population is homogeneous and although sharing levels for HIV appear to be well below the critical levels, there may be some subgroups of the population where the level of sharing exceeds this threshold resulting in a maintained high prevalence and incidence of infection within these groups. The model incorporates the transmission of HCV through sharing of injecting paraphernalia and other sources by incorporating a single rate of new infections that result from non-needle and syringe sharing contact. Data on the number of HCV infections resulting from sexual intercourse or through the sharing of injecting paraphernalia is limited and thus makes parameter estimation exceedingly difficult. The paper does not make it clear how important these other sources are in the model and the level of detail makes it impossible to determine whether these sources are viable routes for HCV transmission.

The model of Vickerman *et al.* (2009)

Vickerman *et al.* (2009) developed deterministic compartmental models to simulate the transmission of HCV and HIV amongst IDUs in Rawalpindi, Pakistan with different levels of needle and syringe sharing. The model was used to investigate why the prevalence of HCV amongst IDUs in Rawalpindi was low despite the widespread reporting of needle and syringe sharing. In addition, the model was used to project the future HCV and HIV epidemics and estimate the potential impact of a generic intervention measure, which reduces the level of needle and syringe sharing, on the prevalence of HCV and HIV amongst the IDU population.

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

further assumed that IDUs can leave this population at any stage at a constant per capita rate if they cease injecting, die due to overdose or experience severe HIV related morbidity.

In the HIV model, the authors continued to stratify the population by frequency of needle and syringe sharing and length of injecting career. This model assumed that once a susceptible IDU is infected with HIV they progress to a stage of infection where they have high levels of HIV viraemia. They are then assumed to progress to a longer lasting infectious class where they have much lower levels of HIV viraemia. Finally, the infected IDU progresses to another stage of infection with high levels of HIV viraemia, after which they develop AIDS.

The model simulated the joint infection status of IDUs and assumed that those with HIV infection were more susceptible to HCV infection, less likely to resolve their HCV infection and less likely to become immune to HCV re-infection. The authors used survey data on IDUs from Rawalpindi during 2007 to obtain epidemiological and behavioural parameter estimates for the model. This survey data was also used to obtain model fits. Biological parameter estimates were obtained from the scientific literature. Since there was some uncertainty surrounding all of the model parameters, for example the HCV transmission probability and the extent that HIV infection increases HCV transmission, the authors used a fitting algorithm to obtain multiple model fits to the survey data for the area. The algorithm sampled 400 parameter sets from the parameter uncertainty space from which five parameter sets were randomly selected and developed into scenarios in order to explore different hypotheses for why HCV prevalence in Rawalpindi was low but HCV-HIV co-infection was high.

For four of the scenarios the IDU population was further stratified into low and high risk groups. IDUs in the low risk group were assumed to share needles and syringes and acquire the majority of their needles and syringes from a reliable source such as a pharmacy, shop, hospital or health worker. IDUs in the high risk group were assumed to share needles and syringes and acquire the majority of their needles and syringes from unreliable sources such as other IDUs or drug dealers. For the fifth scenario, the IDU population was further stratified by the frequency of sharing with strangers (never share with strangers, share infrequently with strangers and share frequently with strangers). Here, the term strangers refers to people that the IDUs have never shared with before. The

first four scenarios made varying assumptions about the probabilities of disease transmission through the sharing of needles and syringes and were used to examine why the prevalence of HCV was low amongst this IDU population while the frequency of needle and syringe sharing was not. Scenario five was developed to examine whether the sharing of needles and syringes with strangers could reproduce the high prevalence of HCV-HIV co-infection observed amongst a small group of IDUs.

For each simulation, the HCV transmission model was run until the prevalence of HCV amongst the IDU population reached its endemic equilibrium prevalence. If the simulated prevalence was below the upper bound of the surveyed HCV prevalence estimate the HIV model was run for a period of 2-12 years (the duration of the HIV epidemic in this area prior to survey). If the prevalence of HCV and the prevalence of HIV were within the 95% confidence intervals suggested by the survey the authors considered the run as a fit. The validity of each fit was determined by how well the fit replicated the prevalence of HCV amongst HIV infected IDUs. The accuracy and validity of all the model fits were used to determine which scenario best explained the HCV and HIV epidemics in this area of Pakistan.

Results

The authors found that only one of their scenarios could reproduce the observed HCV and HIV prevalences. The results 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 IDUs that share more frequently with strangers, hence the high prevalence of HCV-HIV co-infection. Furthermore, the model results suggested that HIV prevalence would increase over a period of 5-10 years if there was no change in the risk behaviour of these IDUs. In addition, the future prevalence of HCV was found to depend on the effect that HIV infection has on the transmission probability of HCV. If there was no effect then a decrease in HCV prevalence would be observed. If HIV co-infection resulted in a two-fold increase in the infectivity of HCV then an increase in HCV prevalence would be observed. Finally, any intervention measures employed to reduce the sharing of needles and syringes would need to achieve a sustained and substantial reduction ($> 40\%$) 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. These intervention measures should also reach high risk IDUs.

Limitations of this research

This modelling work highlighted the importance of preventing the spread of infections amongst IDU populations in a low prevalence setting. The authors mentioned in their discussion that it was difficult to parameterise the model because of the insufficient data or the uncertainty surrounding all the model parameter estimates. This could mean that the true potential of any intervention or the true behavioural characteristics that result in the observed HCV and HIV prevalences are masked by the large amount of uncertainty surrounding certain parameters. In addition, the predictions on the impact of the intervention measure are for a period of ten years. This means that the authors had to assume that there was no change in risk behaviour of the IDU population during this time. It is possible that a scarce supply of drugs or dealers or a change in attitudes may result in IDUs changing their injecting risk behaviour. Any such change in injecting risk behaviour may reduce the estimated potential of any intervention measure employed in this population. Finally, the model used here does not consider the possibility that HCV transmission could occur through the sharing of drug preparation equipment.

This completes our survey of models that examine the spread of both HCV and HIV amongst IDUs. In the next section we shall look at further models which examine the effect of control measures on HCV in an IDU population.

1.12.2 Models that examine the potential impact of intervention measures of the spread of HCV amongst IDUs

In this section we further look at models which study the impact of control strategies on HCV transmission. There are two of these. The first one is by Hutchinson, Bird *et al.* (2006). The second is by Vickerman *et al.* (2007).

The model of Hutchinson, Bird *et al.* (2006)

Hutchinson, Bird *et al.* (2006) used a stochastic simulation to model the transmission of HCV in Glasgow IDUs through the sharing of used needles and syringes. The authors used their model to estimate the prevalence and incidence of HCV among Glasgow IDUs during 1960-2000. Estimates of prevalence and incidence during 1988-2000 were used to determine the number of infections that intervention measures had prevented during this period. The model was also used to explore the effect of incorporating a ten-fold increase in the infectivity of HCV during a short six to eight week period following initial infection.

The model allowed IDUs to move through three infectious stages: susceptible, acute HCV infection and chronic HCV infection. The acute phase of HCV infection was separated into a short non-infectious phase and an infectious phase, lasting up to two years. In addition, the model allowed IDUs to spontaneously resolve their acute HCV infection, rendering them uninfectious but susceptible to HCV re-infection.

The authors assumed that IDUs entered and left the population on random days throughout the year. Members of the IDU population were randomly selected, with equal probability, to leave the needle and syringe sharing population. Susceptible IDUs, once infected with HCV, progressed to the non-infectious acute phase. After their time in this class they progressed to the infectious acute stage of infection. From here they could either resolve their infection and return to the susceptible class or they could develop chronic HCV infection. The IDUs who resolved their infection were assumed to have partial immunity to HCV re-infection. In line with studies by Farci *et al.* (1992) and Mehta *et al.* (2002) the authors assumed that these IDUs were half as likely to develop new HCV viraemia and twelve times less likely to develop chronic HCV infection.

Community-wide surveys of IDUs in Glasgow during 1990-94 and 1999 were used to provide estimates on the frequency of injecting and needle and syringe sharing. A similar survey of IDUs in Edinburgh during 1992-1993 was used to estimate the proportion of IDUs who shared at least once. For simplicity the authors assumed that IDUs injected three times a day for a period of 48 weeks during 1960-1994 or 40 weeks during 1995-2000. The increase in the period of abstinence was incorporated to allow for an increase in the number of IDUs that

were prescribed methadone. On a given day, the number of times that an IDU shared needles and syringes from their three daily injections was randomly assigned using a binomial distribution with probability equal to the fraction of their total injections which were shared injections. Furthermore, for each sharing event that occurred, the person that the IDU shared with was randomly assigned from the sharing partners of that individual. Each sharing partnership was assumed to last for one year.

Results

Simulations were on an individual basis and tracked the daily transmission of HCV amongst Glasgow IDUs. Simulation results were compared to the HCV prevalence estimates obtained from community-wide surveys of IDUs in Glasgow. Significantly more of the simulations obtained from the model which assumed the ten-fold increase in infectivity produced HCV prevalences that were within the ranges suggested by the surveys ($p = 0.001$). The best fitting, high infectivity, simulation was used to produce HCV incidence estimates. The incidence of HCV infection was estimated to be 6-40 per 100 person-years during 1960-1976, 78-89 per 100 person-years during 1977-1986 and 18-30 per 100 person-years during 1990-2000.

In order to determine the number of infections that had potentially been prevented as a result of intervention measures, the authors applied the high levels of needle and syringe sharing from the early to mid 1980s to the period 1988-2000. The median cumulative number of newly infected IDUs generated from this model were then compared to the results from the model without this high risk behaviour. Scenario analyses found that, during the period 1988-2000, approximately 4,500 infections (10th-90th percentiles: 2,400-7,700) had potentially been prevented as a result of intervention measures. Furthermore, the authors found that restricting equipment sharing to one person could have prevented an estimated 5,300 infections (10th-90th percentiles: 4,100-6,700) over the same period.

Limitations of this research

This modelling work used self-reported needle and syringe sharing data to parameterise the model. It is possible that IDUs under-report their needle and syringe sharing and this potential bias could result in the model over-estimating the impact that the intervention measures have had on HCV incidence. In their discussion the authors mention that more data is needed to refine their estimates relating to the incidence and cessation of injecting drug use. This would serve to make the model predictions more accurate. The cleaning of needles and syringes was not considered in this model nor was the possibility that HCV can be transmitted through the sharing of other injecting paraphernalia. Therefore, the model may have over-estimated the number of infections that had potentially been prevented by the intervention measures.

The model of Vickerman *et al.* (2007)

Vickerman *et al.* (2007) used a deterministic compartmental model to describe the transmission of HCV amongst London IDUs. The model simulated the dynamics of HCV infection over the length of injecting career of the IDUs and was used to explore the impact of intervention measures that reduced needle and syringe sharing in all IDUs, IDUs who have been sharing needles and syringes for more than one year, and IDUs with low or high frequencies of needle and syringe sharing. The transmission of HCV through the sharing of injecting paraphernalia and the sexual transmission of HCV was not considered in this work.

The model structure allowed for two acute HCV infectious classes, one for those IDUs who could spontaneously resolve their acute infection and one which allowed IDUs 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.

Susceptible IDUs, once infected with HCV, are assumed to enter an acute phase of infection. The authors assumed that a proportion of these newly infected IDUs progress to the acute stage of infection which allows IDUs to spontaneously resolve their infection. The remaining proportion of these newly infected IDUs are assumed to progress to the acute stage of infection which develops into chronic HCV infection. The IDUs who spontaneously resolve their acute HCV infection

are assumed to be immune to re-infection with HCV for life. It is assumed that IDUs who develop chronic HCV infection remain infected for life. It is further assumed that IDUs can leave the sharing, injecting population at any time at a constant per capita rate due to death or cessation of injecting behaviour.

In addition to stratifying the population by HCV infection status, the authors divided the IDU population into three behavioural subgroups depending on their needle and syringe sharing frequency. Therefore, the IDU population is separated into those that do not share needles and syringes, those who share needles and syringes infrequently and those who frequently share needles and syringes. IDUs 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.

The model also allowed IDUs who are recent initiates to injecting drug use (those who have been injecting for less than one year) to have a greater frequency of needle and syringe sharing and to share occasionally with older IDUs.

Where possible, the authors used published literature sources as well as cohort studies and routine surveillance data from London in 2002-2003 to parameterise the model. However, the uncertainty surrounding some parameter estimates as well as the lack of sufficient data for some parameters meant that the authors had to use proxy estimates and large uncertainty bounds for some parameters.

The model was run for 1,000 parameter sets that were randomly sampled from the parameter uncertainty space. For each parameter set, the chi-squared error between the model behaviour and the epidemiological data was calculated. Then, using the Newton's method numerical algorithm to minimise the chi-squared errors, 30 best fits of the model to the epidemiological survey data from London during 2002-2003 were obtained. These 30 best fits were then grouped into four different classes based on their common attributes. For each class, the simulation with the smallest chi-squared error was used in the analysis.

Results

Results showed that large sustained reductions in sharing rates (greater than 50%) would reduce HCV seroprevalence in IDUs injecting for more than eight years and modest reductions (less than 25%) would reduce HCV in those IDUs injecting for less than four years. In order to reduce HCV prevalence to less than

10% the simulations showed that needle and syringe sharing rates would have to reduce from the baseline estimate of 16 events per month to one to two events per month. Furthermore, the model results also suggested large reductions in HCV seroprevalence would only be achieved if interventions were aimed at all IDUs and reached them within their first year of injecting.

Limitations of this research

This modelling work provided insights into the difficulties in controlling the spread of HCV amongst IDUs and the importance of ensuring that interventions to reduce needle and syringe sharing reached all IDUs, including those who are within their first year of injecting. However, these projections assumed that the reduction in needle and syringe sharing is maintained over the course of the injecting careers of the IDUs. Any change in the risk behaviour of IDUs over this time period may result in reducing the projected impact of the intervention measures. The uncertainty surrounding some parameter estimates meant that it was not possible to determine which of the model fits was more realistic. More reliable parameter estimates would help refine the model selection and allow for a more accurate evaluation on the effectiveness of intervention measures to reduce the sharing of needles and syringes amongst IDUs in London.

The model did not allow IDUs to be re-infected with HCV and did not consider the possibility of HCV transmission through the sharing of drug preparation equipment. This omission could result in the model over-estimating the impact that the intervention measure would have on the prevalence of HCV.

This concludes our discussion on the two models which study the impact of control strategies on HCV spread. In the next subsection we review the information on the models discussed in Section 1.12.

1.12.3 Conclusions

In Section 1.12 we reviewed models which approximated the spread of HCV amongst IDUs through the sharing of needles and syringes. A search of titles, abstracts and keywords was conducted using three databases found a small number of papers which specifically modelled the transmission of HCV amongst IDUs

through the sharing of needles and syringes. These studies focused on IDU populations in Australia (Murray *et al.* 2003), Glasgow (Hutchinson, Bird *et al.* 2006), London (Vickerman *et al.* 2007) and Pakistan (Vickerman *et al.* 2009).

Three out of the four models discussed in Section 1.12 were deterministic mathematical models which examined the impact of control strategies on the spread of HCV amongst IDUs (Murray *et al.* 2003; Vickerman *et al.* 2007; Vickerman *et al.* 2009). The fourth model, (Hutchinson, Bird *et al.* 2006), was a stochastic simulation model which also examined the impact of control strategies on HCV spread amongst IDUs.

It is clear from our discussions that the model structure varied between the articles. Hutchinson, Bird *et al.* (2006) allowed IDUs who had spontaneously cleared an infection to develop partial immunity to HCV re-infection and persistence whereas Vickerman *et al.* (2007, 2009) included an immune state in their models. In contrast to these models, Murray *et al.* (2003) did not allow IDUs to resolve their HCV infection and did not differentiate between acute and chronic HCV infection.

Although Murray *et al.* (2003) modelled HCV infections caused by non-needle and syringe sharing contact, their single rate of infection did not allow further examination of the validity of these transmission sources and did not differentiate between the risks posed by sexual exposure to HCV and the risks posed by the sharing of drug preparation equipment.

Despite the differences in these models, they all required estimates of key biological and behavioural parameters, particularly transmissibility and the clinical course of infection. These parameters are often uncertain due to difficulties in their estimation, and thus could affect the model predictions. Although Vickerman *et al.* (2007, 2009) used fitting algorithms to aid in the parameter estimation process, their work highlighted that this may involve a large number of parameters which could invalidate or limit the model results.

1.13 Discussion

In this chapter we have presented the results of a literature review of the epidemiology and modelling of HCV, as well as a more general overview of the techniques used to model infectious diseases. HCV is a major health problem that affects

millions of people worldwide; the majority of the three to four million new cases each year progress to chronic HCV infection which is associated with an increased risk of developing severe liver disease (Seef 2002; World Health Organisation 2000; Kamal 2008). 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).

HCV is primarily transmitted through blood to blood contact, with the majority of infections in resource-rich countries attributed to a history of injecting drug use (Thorpe *et al.* 2002; Bialek and Terrault 2006). In fact, IDUs are more at risk of contracting HCV than HIV through the sharing of needles and syringes (Garfein *et al.* 1998; Hagan and des Jarlais 2000). The Scottish Executive have recognised that the high prevalence of HCV amongst IDUs in Scotland is a serious pubic health risk and substantial resources have been allocated to improve intervention methods aimed at preventing the transmission of HCV in the IDU population (Scottish Executive 2008b).

Mathematical models, such as those developed in this thesis, can be used to provide valuable insight into how infectious diseases spread as well as to evaluate the effectiveness of intervention measures and highlight the requirements necessary to achieve disease elimination. There are many different model structures, and in this review we have highlighted some of the more common structures, including deterministic, stochastic, SIS, and SIR models. Examples were presented to illustrate how these models have been used.

Since there are many similarities between how HCV and HIV spread amongst IDUs, many of the techniques used to develop and analyse HIV models can be applied to HCV models. Therefore, we reviewed several mathematical models of the spread of HIV amongst IDUs prior to reviewing the four models of HCV transmission amongst IDUs available in the published literature.

In order to develop accurate to models of the spread of HCV amongst IDUs, it is important that we fully understand the dynamics of the disease. In the next chapter of this thesis we shall present the results of a systematic review of the literature which examined key issues for the modelling HCV epidemics amongst IDUs and the impact of intervention measures.

Chapter 2

Risk of HCV re-infection following spontaneous viral clearance in injecting drug users: A systematic review

2.1 Introduction

HCV is a viral infection of the liver, whose mode of transmission is through blood to blood contact. Since the introduction of blood screening in resource-rich countries, it is the IDU population that is at greatest risk of contracting the disease through the sharing of injecting equipment (Bialek and Terrault 2006). IDUs are more at risk of contracting the HCV than HIV (Garfein *et al.* 1998; Hagan and des Jarlais 2000), therefore recent recommendations to improve intervention coverage in this population have focused on the prevention of HCV infection (Scottish Executive 2008a; Advisory Council on the Misuse of Drugs 2009).

A few studies have modelled the spread of HCV among IDUs and demonstrated the potential effectiveness of interventions, such as needle exchange and other harm reduction measures (Murray *et al.* 2003; Hutchinson, Bird *et al.* 2006; Vickerman *et al.* 2007, 2009). These models however rely on accurate estimates of key biological parameters such as transmissibility of the virus and the clinical course of infection.

Of individuals with newly acquired HCV, a proportion spontaneously recover from their acute infection. A systematic review of longitudinal studies involving almost 700 persons with acute HCV infection estimated that the rate of spontaneous viral clearance was 26%, 95% CI 22-29%, (Micallef *et al.* 2006). The remaining proportion with newly acquired HCV infection go on to develop chronic infection and are at risk of complications such as liver failure and liver cancer.

Some studies have suggested that partial immunity to HCV re-infection and persistence may be acquired in individuals who have spontaneously cleared a previous infection (Farci *et al.* 1992; Mehta *et al.* 2002). In line with these studies, Hutchinson, Bird *et al.* (2006) assumed, in their model of HCV transmission among IDUs, that those who cleared a previous infection were half as likely to develop new viraemia following re-exposure and were twelve times less likely to develop chronic infection. In contrast to previous evidence, a recent study found that HCV (re-)infection among IDUs was more likely among those who had cleared a prior infection than in HCV-naive individuals, which may imply no increased immunity to HCV re-infection (Aitken, Lewis *et al.* 2008). Vickerman *et al.* (2007, 2009) included an immune state in their model of HCV transmission, based on that developed by Kretzschmar and Wiessing (2004).

Given the differences in the structure of HCV transmission models among IDUs which have been applied in the past (Hutchinson *et al.* 2006; Vickerman *et al.* 2007, 2009), and the conflicting evidence reported in the literature (Mehta *et al.* 2002; Aitken, Lewis *et al.* 2008), a systematic review was undertaken to determine to what extent:

(i) the rate of acute HCV infection differs between susceptible IDUs who have spontaneously cleared a previous infection and those who have not previously been infected;

(ii) the rate of chronic HCV infection (following a recent acute infection) differs between IDUs who have spontaneously cleared a previous infection and those who have not previously been infected; and

(iii) IDUs develop immunity to HCV re-infection with either the same or all genotypes.

2.2 Methods

2.2.1 Search strategy and inclusion criteria

A literature search of PUBMED (January 1950 to January 2009), EMBASE (January 1980 to January 2009) and PsycINFO (January 1967 to January 2009) was performed to identify English language, primary research papers involving the longitudinal assessment of IDUs, that have either

(a) compared the rate of acute HCV infection between those who have spontaneously cleared a previous infection and those who have not been previously infected;

(b) compared the rate of chronic HCV infection between those who have spontaneously cleared a previous infection and those who have not been previously infected;

(c) examined HCV re-infection with the same or different genotype.

Here, those who have spontaneously cleared a previous infection referred to those who test HCV antibody positive and HCV RNA negative, while those who have not previously been infected referred to those who test HCV antibody negative and HCV RNA negative. Any generation of antibody or RNA test was considered to ensure all relevant studies were included.

For (a) and (c), individuals had to have been at risk of acquiring HCV infection through continued injecting drug use during follow-up. For (a) and (b), HCV RNA had to have been measured and reported for all study subjects during follow-up; while for (c) HCV RNA and genotype had to be measured and reported for all study subjects during follow-up. Studies involving individuals who had undergone either HCV antiviral therapy (treatment) or transplantation were excluded. The following search terms were used:

1. HCV or Hepatitis C

2. Reinfect$ or Immun$ or Rechall$ or Reexpos$ or Clear$ or Eliminat$ or Resist$ or Protect$ or Second$ Infect$ or Consecutive Infect$ or Persistent Infect$ or Previous$ Infect$ or Multiple Infect$

3. (1) and (2)

where the $ symbol allows terms to be truncated thus giving all variant spellings or word endings from the symbol onwards.

A panel of three (Stephen Corson, Norah Palmateer, and Amanda Weir) independently reviewed the abstracts identified from the literature search, and selected papers for full text review based on the above inclusion and exclusion criteria. Full text articles were independently reviewed by each of the three panel members; in addition, references in selected articles which were not identified through the original search were examined and included if relevant. The following information was extracted from each article: country of study, calender years of recruitment, method of recruitment and follow-up, laboratory tests performed, number of study subjects, age and gender distribution, prevalence of HIV infection, duration of follow-up, definitions relating to study subjects and outcome measures, study limitations reported by authors, and data on one or more of the following outcome measures:

(i) rate of acute HCV infection,

(ii) rate of chronic HCV infection and,

(iii) HCV re-infection with the same or different genotype.

2.3 Results

The initial search yielded 4,594 articles (Figure 2.1); of these, 4,506 were excluded for the following reasons: duplicate articles (identified through searching multiple databases), not primary research papers, study subjects were not IDUs, and articles did not address the review questions. The remaining 88 abstracts were independently reviewed by the panel: 76 were excluded and 12 retained for full text review. Following the full text review, nine articles were excluded because either subjects were not IDUs, subjects were not at risk of re-infection, there was no evidence relating to the review questions, subjects had undergone treatment, or HCV genotype was not reported. Thus, three articles, involving a total of 2,145 subjects from studies conducted in Australia and the United States were

included in this review; the recruitment and follow-up methods applied in these studies are summarised in Table 2.1.

2.3.1 Comparison of the rate of acute HCV infection between IDUs who have previously cleared infection and those not previously infected

The systematic review identified three studies (Mehta *et al.* 2002; Micallef *et al.* 2007; Aitken, Lewis *et al.* 2008) that compared the rate of acute HCV infection between IDUs who have previously cleared infection and those not previously infected (Table 2.2).

The earliest published study by Mehta *et al.* (2002) compared the occurrence of viraemia (defined as the detection of HCV RNA during follow-up) between two groups of IDUs from Baltimore over four consecutive six month periods: (i) 98 subjects who were HCV-antibody positive at study enrolment and whose HCV RNA was undetectable at two consecutive visits (previously infected) and (ii) 164 subjects who were HCV-antibody negative and HCV RNA negative at study enrolment (previously uninfected).

This study found that the development of viraemia was lower in the previously infected group (12% of 98 subjects) than in the previously uninfected group (21% of 164 subjects), $p = 0.07$. After adjustment for "drug use practices" (not further specified), those with previous HCV infection were half as likely (hazard ratio 0.45, 95% CI 0.23-0.88) to develop new viraemia than those previously uninfected.

Through retrospective testing, Micallef *et al.* (2007) found that the incidence of HCV re-infection (detection of HCV RNA during follow-up) among 18 subjects who were previously infected (31 per 100 person-years, 95% CI 17-62) was higher than that of initial infection among 423 subjects who were previously uninfected (17 per 100 person-years, 95% CI 14-20). After adjustment for the major drug injected, sharing of equipment, and incarceration, an incidence rate ratio of HCV re-infection to initial infection of 1.11 was obtained, though this ratio was not statistically significant ($p = 0.8$).

The most recent study by Aitken, Lewis *et al.* (2008) followed subjects who had provided a blood sample at least twice at approximately three month intervals. This

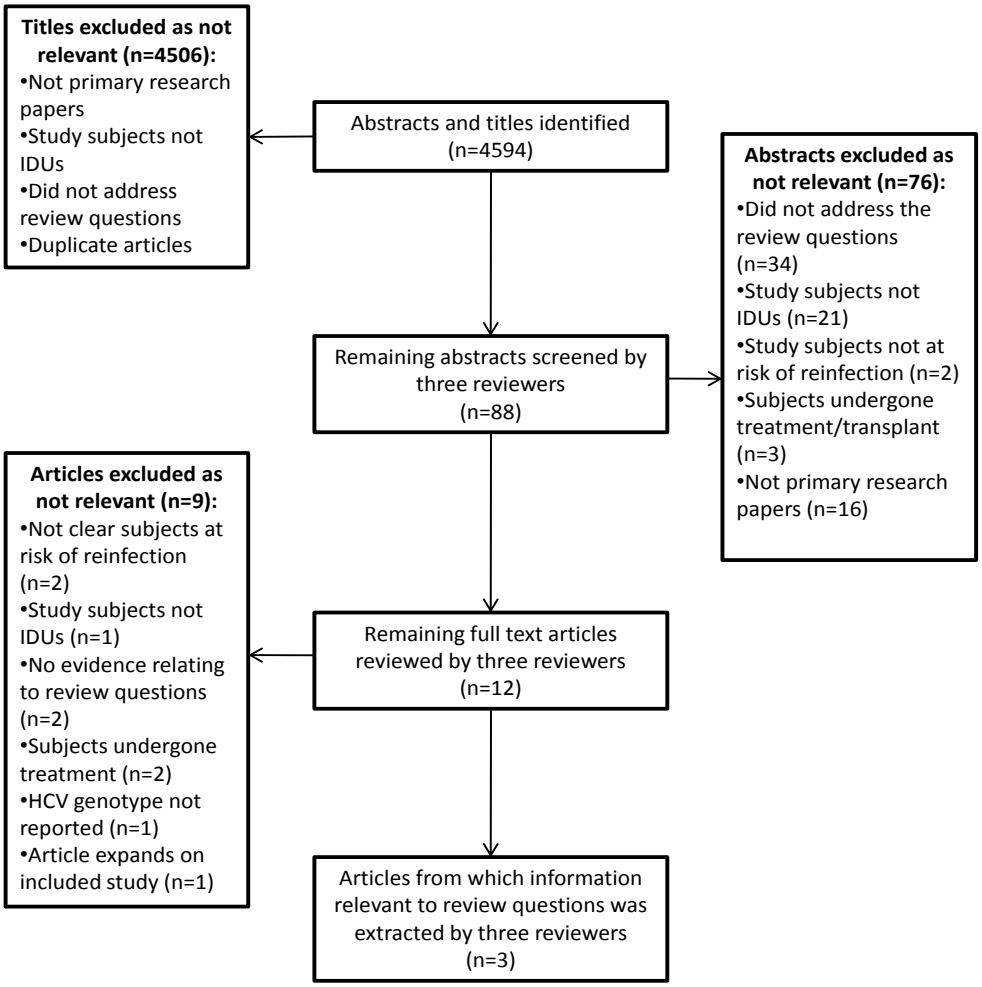

Figure 2.1: Flow diagram detailing systematic review process.

Author/ Reference	Country	Recruitment Method	Overall Sample Size	Calendar Years of Recruitment	Follow-Up Method	Laboratory Tests	
						Antibody Test	RNA Test
Mehta *et al.* (2002)	United States	Cohort formed from IDUs recruited to ALIVE study using leaflets distributed at places frequented by IDUs	1,508	1995-1996	Questionnaire data and serum sample collected and tested for HCV RNA at 6-month intervals	2^{nd} or 3^{rd} generation enzyme immunoassay with confirmation by recombinant immunoblot assay	2^{nd} generation branched DNA assay, and Cobas amplicor assay
Micallef *et al.* (2007)	Australia	Retrospectively tested stored serum samples from drug treatment centre	441	1993-2002	Longitudinal HCV RNA testing on stored serum samples	Duplicate testing by 2^{nd} and 3^{rd} generation enzyme immunoassay	Versant HCV RNA assay version 3.0
Aitken, Lewis *et al.* (2008)	Australia	Social networks*	196	2005-2007	Questionnaire data and blood sample collected and tested for HCV RNA at 3-month intervals	3^{rd} generation enzyme immunoassay with confirmation by Murex anti-HCV assay version 4.0	Cobas amplicor assay version 2.0

*Each IDU is asked to describe the relationships between them and their injecting partners and to introduce their partners to researchers.

Table 2.1: Summary of articles included in systematic review.

Author/Reference	Definition of study group	Sample Size	Number (and %) HIV^+	Length of follow-up (years)	Age at recruitment (years)	% Male	Number (and %) with Acute HCV infection† during follow-up	Incidence per 100 person-years (95% CI**)
Mehta *et al.* (2002)	Previously uninfected IDUs (HCV Ab^- & RNA^- at index visit)	164	17 (10%)	median 2.35	mean 31.5	74%	35 (21%)	8.6††
	Previously infected* IDUs (HCV Ab^+ & RNA^- at index visit)	98	36 (37%)	median 2.14	mean 41.1	59%	12 (12%)	5.4††
Micallef *et al.* (2007)	Previously uninfected IDUs (HCV Ab^- & RNA^- at baseline)	423	NA	median 1.00	median 23.0	39%	114 (27%)	17 (14-20)
	Previously infected* IDUs (HCV Ab^+ & ≥ 1 RNA^- at baseline, previously Ab^+ & RNA^+)	18	NA	median 1.20	median 23.0	39%	13 (72%)	31 (17-62)
Aitken, Lewis *et al.* (2008)	Previously uninfected IDUs HCV (Ab^- & RNA^- at baseline)	55	NA	median 0.27	mean 24.6	66%	10 (19%)	15.5 (8.3-28.8)
	Previously infected* IDUs HCV (Ab^+ & RNA^- at baseline)	50	NA	median 0.27	mean 26.8	56%	23 (46%)	46.8 (31.1-70.3)

*IDUs who have spontaneously cleared an HCV infection.
**95% Confidence Interval.
† Tested positive for HCV RNA during the follow-up period
†† Information obtained from Dore and Micallef (2007)
NA Data not available in article.

Table 2.2: Data from review articles on the rate of acute HCV infection between IDUs who have previously cleared infection and those not previously infected.

study found that the rate of infection among the 50 study subjects with evidence of a previous infection (47 per 100 person-years, 95% CI 31-70) was significantly higher than the rate of infection among the 55 study subjects with no evidence of previous infection (16 per 100 person-years, 95% CI 8-29). After adjustment for behavioural and other variables, the rate of infection was 2.54 times (95% CI 1.11-5.78, $p = 0.027$) higher among those previously infected than those previously uninfected.

2.3.2 Comparison of the rate of chronic HCV infection between IDUs who have previously cleared infection and those previously uninfected

The systematic review identified two studies (Mehta *et al.* 2002; Aitken, Lewis *et al.* 2008) that compared the rate of chronic HCV infection between IDUs who have previously cleared infection and those previously uninfected (Table 2.3). Although the number of subjects involved in these studies was small, both Mehta *et al.* (2002) and Aitken, Lewis *et al.* (2008) reported a lower rate of chronic HCV infection among those with evidence of previous HCV infection, compared to those previously uninfected.

Author/Reference	Definition of study group	Sample Size	Length of Follow-up	Number (and %) with chronic HCV infection during follow-up†
Mehta *et al.* (2002)	Previously uninfected IDUs (Ab^- & RNA^- at index visit)	32	median 2.35 years	27 (84%)
	Previously infected* IDUs (Ab^+ & RNA^- at index visit)	9	median 2.14 years	3 (33%)
Aitken, Lewis *et al.* (2008)	Previously uninfected IDUs (Ab^- & RNA^- at baseline)	7	mean 0.93 years	5 (71%)
	Previously infected* IDUs (Ab^+ & RNA^- at baseline)	22	mean 0.91 years	13 (59%)

*IDUs who have spontaneously cleared an HCV infection.
† Tested positive for HCV RNA during follow-up period.

Table 2.3: Data from review articles on the rate of chronic HCV infection between IDUs who have previously cleared infection and those not previously infected.

Mehta *et al.* (2002) showed that the frequency of chronic HCV infection (defined as those who had tested HCV RNA positive at two consecutive visits during follow-up) was significantly lower in subjects with evidence of previous

HCV infection (33%) than in those previously uninfected (84%) (odds ratio 0.09, 95% CI 0.02-0.5, $p = 0.006$).

Aitken, Lewis *et al.* (2008) also found a lower frequency of chronic HCV infection among those with a previous HCV infection (59%) compared to those previously uninfected (71%) although this difference was not significant ($p = 0.7$).

2.3.3 Evidence of HCV re-infection with either the same or different genotype

The systematic review identified two studies (Micallef *et al.* 2007; Aitken, Lewis *et al.* 2008) that examined the extent of HCV re-infection with either the same or a different genotype among IDUs who had previously cleared a HCV infection (Table 2.4).

Author/Reference	Sample Size	Length of Follow-Up	Age (years)	% Male	Number of subjects with evidence of HCV re-infection:			Number of subjects without re-infection
					Same Genotype	Different Genotype	Unknown Genotype	
Micallef *et al.* (2007)	18	median 1.2 years	median 23	39	5	7	1	5
Aitken, Lewis *et al.* (2008)	50	median 0.27 years	NA	NA	5	6	12	27

NA Data not presented in article.

Table 2.4: Data from review articles on evidence of HCV re-infection with either the same or different genotype.

In the first study by Aitken, Lewis *et al.* (2008) 23 HCV re-infections were found among 50 IDUs followed-up for a median of 99 days (range 26-288 days), and eleven of these had genotype information: six were classified as being of a different genotype to that of a previous infection, while five were classified as being of the same genotype. Furthermore, from these eleven IDUs with genotype information, Aitken, Tracy *et al.* (2008) report on one particular subject who was re-infected with three different genotypes over a period of 449 days; each re-infection was preceded by at least one HCV RNA negative test result.

Micallef *et al.* (2007) reported thirteen HCV re-infections among eighteen IDUs followed up for a median of 1.2 years (range 0.3-3.6 years); twelve of these had genotype information: five were classified as being of the same genotype to that of a previous infection, while seven were classified as being of a different genotype.

2.4 Discussion

Mathematical models are increasingly used to inform policy makers on the effectiveness of intervention strategies to prevent of the spread of infectious diseases (Kaplan and O'Keefe 1993; Granich *et al.* 2009). Critical to this process, these models must accurately represent the important epidemiological and disease properties of the condition in question. This systematic review tackled an area of uncertainty regarding the spread of HCV among IDUs, specifically the risk of HCV re-infection and persistence in this population. We acknowledge though that the scope of the review may be limited by the inclusion of only English language studies.

2.4.1 Risk of acute HCV re-infection among IDUs

The three studies included in the systematic review which examined the rate of acute HCV infection between IDUs who have previously cleared their infection and those previously uninfected (Mehta *et al.* 2002; Micallef *et al.* 2007; Aitken, Lewis *et al.* 2008) reported conflicting results: Mehta *et al.* (2002) reported a significantly lower rate, Micallef *et al.* (2007) reported no significant difference, and Aitken, Lewis *et al.* (2008) reported a significantly higher rate among the former compared to the latter group.

There are a number of factors relating to the design of the study and composition of the study population, which may account for the differences in the findings reported by the three studies. In terms of study design, the interval at which IDUs were sampled, the size of the sample studied, the approach to testing and laboratory tests performed varied across the three studies. The heterogeneous sampling frames employed by the three studies may have resulted in differences in the detection (and therefore non-detection) of HCV viraemia between studies. The duration of HCV viraemia in individuals exhibiting spontaneous viral clearance is generally less than 12 weeks (Gerlach *et al.* 2003). Thus, ideally samples from IDUs would need to be collected frequently, on a weekly to monthly basis, to accurately capture data on the development of HCV viraemia. The shorter three monthly sampling interval used by Aitken, Lewis *et al.* (2008) may therefore have resulted in a higher detection of HCV viraemia, particularly among those who had previously cleared their HCV infection (because this group is also

more likely to clear HCV again, based on other evidence in this review), than in the other study by Mehta *et al.* (2002) which employed a longer six monthly sampling frame.

In terms of sample size, the studies identified were only sufficient to detect a statistically significant difference in the presence of HCV viraemia of the order of 15-30% between those previously infected and uninfected. A particularly small number of participants, as few as 18 in the study by Micallef *et al.* (2007), were included in the previously infected group, which weakens also the generalisability of the findings of these studies.

Micallef *et al.* (2007) relied on retrospective testing of serum samples which were stored at −20 degrees C. A decrease in HCV RNA titre has been observed in sera stored at −20 degrees C, whereas long-term stability in HCV RNA was observed at −80 degrees C (Halfon *et al.* 1996). Thus, the storage of samples in the Micallef *et al.* study could have resulted in non-detection of HCV viraemia and under-estimation of the incidence of infection compared to the other two studies (Mehta *et al.* 2002; Aitken, Lewis *et al.* 2008). It is uncertain to what extent the range of laboratory tests performed may have generated different results between studies, but it is unlikely that this explains the conflict in findings between studies.

In terms of the composition of the study population, the age and gender distribution, calender years of observation, continued injecting drug use, and other risk factors for HCV infection varied across the studies. In Mehta *et al.* the previously uninfected cohort was younger (mean age 31.5) than the previously infected cohort (mean age 41.1) and also less likely to be infected with HIV (10% compared to 37% respectively), had a greater proportion of male IDUs (74% compared to 59% respectively), while both Micallef *et al.* and Aitken, Lewis *et al.* compared cohorts of those previously infected and uninfected with similar age and gender distributions (Table 2.2). The differences in age and gender distribution and co-infection with other blood-borne viruses may contribute to the difference in the findings of the studies since, for example, younger IDUs have been found to have higher levels of risk behaviour (Hutchinson *et al.* 2000). Therefore, it is important to adjust appropriately for differences between cohorts. While Mehta *et al.* do not report that the differences in age, gender and HIV distribution have been accounted for in the regression analysis, they do report that "drug

use practices" were accounted for. Both Micallef *et al.* and Aitken, Lewis *et al.* attempted to account for differences between their previously infected and uninfected cohorts. Micallef *et al.* adjusted for history of incarceration, sharing of injecting equipment and major drug injected, while Aitken, Lewis *et al.* examined the influence of a larger number of predictors on time to infection or re-infection, including gender, age of first injection, drugs injected, needle sharing history, imprisonment history, drug treatment status, housing status, hepatitis B infection status, age, length of injecting career and needle sharing frequency. Aitken, Lewis *et al.* found the significant predictors were infection status (previously infected versus previously uninfected), injecting frequency and length of injecting career. While the investigators have therefore tried to identify and adjust for differences between cohort subgroups, the evidence from such observational studies is nevertheless weakened due to the difficulty in accurately capturing data on exposure to HCV (re-)infection through injecting practices and reliance on statistical models to fully account for these differences in the analysis.

A further limitation of the reviewed studies is that none accounted for the possibility of genetic variation in the immune response to HCV, which may contribute to spontaneous viral clearance. Recently published studies have found a strong genetic effect (a polymorphism upstream of the *IL28B* gene) associated with natural clearance of HCV (Thomas *et al.* 2009). Thus, genetic variation may account for the differences in the findings between cohorts in this review and needs to be taken into account in future studies.

To compare the risk of acute HCV between those previously infected and uninfected, it is important that all IDUs in both groups are at risk through continued injecting drug use, as was the case among the three studies included in this review. A further study by Grebely *et al.* (2006) was identified by the literature search but was excluded from the review since the 1,078 study participants were not all engaged in injecting drug use (any, 29%; frequent, 15%). After adjustment for age, sex, ethnicity, HIV infection and housing status this study found that IDUs with previous HCV infection were significantly less likely to develop new infection than those drug users (both injectors and non-injectors) previously uninfected (odds ratio 0.23; 95% CI 0.10-0.51, $p < 0.001$). The methodological issues of this study have been previously highlighted by Dore and Micallef (2007), notably that

(i) the demographic and behavioural differences between the two denominator (uninfected and previously infected) populations may not be adequately adjusted for in the statistical analysis, and

(ii) a relatively long testing interval (greater than six months) may have resulted in non-detection of HCV re-infections.

The results from these small number of studies are conflicting and thus there is no compelling evidence in support of an increased or decreased risk of acute HCV among IDUs who had spontaneously cleared a previous infection compared to those previously uninfected.

2.4.2 Risk of chronic HCV infection among IDUs

The systematic review found two small studies that examined the rate of chronic HCV infection between IDUs who have previously cleared their infection and those previously uninfected (Mehta *et al.* 2002; Aitken, Lewis *et al.* 2008). Data from these studies suggest that there is a lower rate of chronic HCV infection in those who have previously spontaneously resolved their infection. However, the small sample ($<$ 50 IDUs) involved in each study provides limited evidence to support such a conclusion.

2.4.3 Re-infection with either the same or a different genotype among IDUs

The systematic review found two studies that demonstrated that IDUs who spontaneously resolve a previous infection can be re-infected with either the same or a different HCV genotype. Comparable proportions of IDUs were found to be re-infected with either the same or different genotype in both studies, suggesting that the risk of re-infection is not influenced by a past HCV genotype infection. However, further research is needed among larger cohorts of IDUs over longer follow-up periods to accurately quantify the risk of re-infection with different HCV genotypes.

A further study (published in Oct. 2009, subsequent to this review exercise) by van de Laar *et al.* (2009) found that HCV re-infection and superinfection (the latter referring to HCV dual infection) are common among active IDUs. At least

39% of a cohort of 59 HCV seroconverters had evidence of multiple infections over a median seven years follow-up period. The authors, however, suggest that partial protective immunity might result in lower peak viraemia, increased rates of spontaneous viral clearance following re-infection, or protection against strains of the same HCV subtypes.

While there is no doubt that the protective immunity conferred by previous HCV infection is not complete, the findings from the two studies showed that not all IDUs became re-infected during the relatively short follow-up periods (median 0.3 and 1.2 years), and so some may interpret that as a level of protective immunity. While it was not possible to assess the extent to which IDUs were exposed to HCV through continued injecting drug use during follow-up, larger cohort studies would help to inform on the extent of immunity conferred by previous HCV infection.

2.5 Conclusion

This systematic review focused on three key areas relating to the transmission of HCV among IDUs to inform on the development of an accurate disease transmission model, but also importantly help to inform studies of immune protection and vaccine development. The evidence base on the risk of acute and chronic HCV infection in those previously infected with, but having cleared, the virus is limited. More longitudinal studies of IDUs, involving larger cohorts over a longer period of follow-up, need to be designed and implemented to fully understand the dynamics of HCV transmission in this population. Until then, modellers need to take account of the uncertainty in, and understand the contribution of, these key parameters when modelling the spread of HCV infection among IDUs.

This concludes our systematic review. In the next chapter we shall examine a simple mathematical model for the spread of HCV amongst IDUs.

Chapter 3

Simple HCV transmission model

3.1 Introduction

In this chapter we develop a deterministic, compartmental model of HCV transmission through the sharing of needles and syringes. The structure of the model enables IDUs to progress through the various stages of HCV infection, based on the model described previously by Vickerman *et al.* (2007). In contrast to the Vickerman *et al.* (2007) model we model the number of needles and syringes by HCV infection status. Furthermore, we do not consider the treatment of chronically infected IDUs with antiviral therapy and we assume homogeneity in time since onset of injection and needle and syringe sharing rates.

We first derive equations that describe how IDUs and needles and syringes progress through the stages of HCV infection and obtain an expression for the basic reproductive number R_0. An equilibrium and stability analysis is conducted to investigate the behaviour of our model over time, paying particular attention to the conditions necessary for HCV to die out or persist in the IDU population. A brief summary of the main findings concludes the chapter.

3.2 Model description

3.2.1 IDU population

We assume that the IDU population at time t is well mixed and of size n, where n is large and constant. Therefore, when IDUs leave the population (due to either

permanent cessation of injecting behaviour or death) at a per capita rate μ they are immediately replaced by IDUs susceptible to HCV infection.

The IDU population is divided into those IDUs susceptible to HCV infection through needle and syringe sharing (denoted x for those not previously infected, x_1 for those 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 re-infection (z) (Figure 3.1). The model allows for two different types of acute HCV infection: one which leads to chronic infection and the other which leads to self limiting HCV infection.

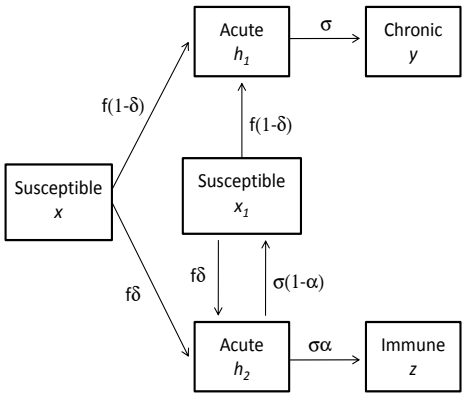

Figure 3.1: HCV transmission flow diagram. The arrows in the diagram indicate the possible transitions for IDUs between stages of HCV infection and the parameters shown are the per capita rate of flow between the stages. The rate of recruitment to the population and the rate at which IDUs leave the population (μ) are not shown.

The force of infection experienced by a single susceptible IDU is given by $f = \lambda(1-\phi)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y)$, where λ is the average rate, per year, that IDUs share needles and syringes; ϕ is the probability that an IDU will successfully clean their needle and syringe prior to use (successful cleaning requires IDUs to clean their injecting equipment with alcohol or bleach so that there is no HCV viral load present prior to use); α_h and α_y are the transmission probabilities per injection

when a single susceptible drug user injects with a single needle in the acute and chronic HCV stages of infection respectively; and β_{h_1}, β_{h_2} and β_y are respectively the fractions of h_1 acutely infected, h_2 acutely infected and chronically infected needles and syringes at time t. The inclusion of differential HCV transmission probabilities relating to acute and chronic infection, as applied by Hutchinson, Bird *et al.* (2006), is also similar to assumptions used in HIV modelling. Based on varying blood viral loads associated with stages of HIV infection (Seitz and Müller 1994), mathematical models of HIV have taken into account high and low probabilities of HIV transmission according to respective periods of acute and chronic infection (Greenhalgh and Lewis 2000). Therefore, it seemed reasonable to include a similar differential risk of HCV transmission in our model.

Susceptible IDUs, once infected with HCV, will progress to the acute stage of infection (either h_1 or h_2). A proportion δ, where $\delta < 1$, of these newly infected IDUs will progress to the acute h_2 class. At the end of their time in this class these IDUs clear the virus spontaneously with a proportion α becoming immune to HCV re-infection and the remaining $(1 - \alpha)$ becoming susceptible to HCV re-infection (Farci *et al.* 1992; Mehta *et al.* 2002; Micallef *et al.* 2007). The remaining proportion $(1 - \delta)$ of newly infected IDUs progress to the acute h_1 class: these IDUs will progress to chronic infection where they will remain until they either die or permanently leave the sharing injecting population.

3.2.2 Needles and syringes

Since our IDU population can exist in different stages of infectivity and it is the blood of the IDU that determines the infectivity of a needle and syringe, it makes sense to allow needle and syringes to have different levels of infectivity. Here we are going to explicitly model the number of needles and syringes (m) by HCV infection status (i.e. either uninfected, acutely infected or chronically infected) over time. We introduce three infectious needle classes (acute h_1, acute h_2 and chronic y), where each class corresponds to the infectivity of an IDU in the acute h_1, acute h_2 and chronic y stages of infection respectively.

If a previously unused needle and syringe (a needle and syringe that is devoid of any fluid) is used by an IDU in the acute h_1 stage of infection, the needle and syringe will be contaminated with acute h_1 HCV. This is the same for a

previously unused needle and syringe that has been used by an IDU in either the acute h_2 stage or the chronic y stage of infection. This leads us to define an acute h_1 needle and syringe to be a needle and syringe, previously unused, that has been used by an IDU in the acute h_1 stage of HCV infection. The acute h_2 and chronic y infectious needle classes are similarly defined.

While these definitions seem reasonable, survey data of IDU risk behaviour clearly shows that IDUs use needles and syringes more than once before they are discarded (NESI 2010). The re-using of needles and syringes implies that it is unlikely that all needles and syringes will be previously unused and hence devoid of any fluid. We must therefore modify the definition of acute h_1, acute h_2 and chronic y needles and syringes to incorporate this risk behaviour.

Consider a previously unused needle and syringe that has been used by an IDU who is susceptible to HCV infection. After the injecting process has been completed this needle and syringe will contain a small amount of blood which is uncontaminated with HCV. Suppose that this needle and syringe is then used by an IDU in the acute h_1 stage of infection. It is possible that the HCV viral load left in this needle and syringe by the acute h_1 IDU will be different to that of a previously unused needle used by an acute h_1 IDU. On the other hand it is possible that the IDU will replace the uninfectious blood with their blood during the injection process, thus leaving the needle and syringe with an HCV viral load similar to that of a previously unused needle and syringe used by the IDU. With no evidence to suggest which situation is more realistic we assume that any difference in the HCV viral load left by an infectious IDU in a used but uncontaminated needle and a previously unused needle is small enough to be ignored meaning that the HCV viral load is the same in both cases. Hence we now define an acute h_1 needle and syringe to be any uncontaminated needle and syringe that has been used by an IDU in the acute h_1 stage of HCV infection. The acute h_2 and chronic y needle and syringe classes are similarly defined.

Now that we have defined our infectious needle and syringe classes we introduce an assumption, corresponding to that adopted by Greenhalgh and Lewis (2000), which makes our model optimistic when compared to other possible assumptions (Greenhalgh and Lewis 2001, 2002) and could be used to obtain a lower bound for the fraction of IDUs and needles and syringes infected with HCV. We assume that the infectivity of each needle and syringe is determined by the infec-

tivity of the IDU who last used the needle and syringe, with needles and syringes that have never been used being uninfectious. For example, an acute h_1 infectious needle and syringe used by an IDU in the chronic y stage of infection will change to the chronic y stage; a chronic y infectious needle and syringe used by a susceptible IDU will become uncontaminated (non-infectious) and an acute h_1 needle and syringe used by an IDU in the acute h_2 stage of infection will change to the acute h_2 stage.

Finally we assume a needle turnover rate (the average rate at which IDUs change their needles for clean needles) of τ per year, IDUs can become infected only through the sharing of needles and syringes used by an HCV acutely or chronically infected IDU and that infectious needles and syringes do not lose their infectivity if they are left unused for a period of time.

3.2.3 Governing equations

We now derive the differential equations which describe the spread of HCV among IDUs where IDUs progress through the various stages of HCV infection described in Subsection 3.2.1 and HCV infection is caused by sharing the three types of infectious needle described in Subsection 3.2.2. We derive a total of nine differential equations: six equations for IDUs and three for needles.

Let $\pi_x(t)$, $\pi_{x_1}(t)$, $\pi_{h_1}(t)$, $\pi_{h_2}(t)$, $\pi_y(t)$, $\pi_z(t)$ denote the fraction of IDUs in the x-susceptible, x_1-susceptible, acute h_1, acute h_2, chronic y and immune z classes at time t. In a similar way $\beta_{h_1}(t)$, $\beta_{h_2}(t)$ and $\beta_y(t)$ denote the fraction of needles at each stage of HCV infection at time t. We define the constant IDU to needle ratio $\gamma = n/m$ to be the number of IDUs per needle in the population.

The number of x-susceptible IDUs at time $t+\Delta t$

$$
\begin{aligned}
&= \text{the number of } x\text{-susceptible IDUs at time } t \\
&+ \text{the number of IDUs recruited to sharing intravenous injecting} \\
&\quad \text{drug use in } [t,\ t+\Delta t) \\
&- \text{the number of } x\text{-susceptible IDUs who develop acute HCV} \\
&\quad \text{infection in } [t,\ t+\Delta t)
\end{aligned}
$$

− the number of x-susceptible IDUs who leave the population due to death or cessation of injecting drug use in $[t,\ t{+}\Delta t)$.

Thus we have

$$\begin{aligned} n\pi_x(t+\Delta t) =& n\pi_x(t) + n\mu\Delta t - \lambda n\pi_x(t)\Delta t(1-\phi)(\alpha_h(\beta_{h_1}(t)+\beta_{h_2}(t)) + \alpha_y\beta_y(t)) \\ & - \mu n\pi_x(t)\Delta t + o(\Delta t). \end{aligned}$$

Subtracting $n\pi_x(t)$ from both sides, dividing by $n\Delta t$ and letting $\Delta t \to 0$ gives

$$\frac{d\pi_x}{dt} = \mu - \mu\pi_x - \lambda\pi_x(1-\phi)(\alpha_h(\beta_{h_1}+\beta_{h_2}) + \alpha_y\beta_y).$$

The number of x_1-susceptible IDUs at time $t{+}\Delta t$

= the number of x_1-susceptible IDUs at time t
+ the number of IDUs who spontaneously resolve an HCV infection in $[t,\ t{+}\Delta t)$
− the number of x_1-susceptible IDUs who develop acute HCV infection in $[t,\ t{+}\Delta t)$
− the number of x_1-susceptible IDUs who leave the population due to death or cessation of injecting drug use in $[t,\ t{+}\Delta t)$.

Thus we have

$$\begin{aligned} n\pi_{x_1}(t+\Delta t) =& n\pi_{x_1}(t) + \sigma(1-\alpha)n\pi_{h_2}(t)\Delta t - n\mu\pi_{x_1}(t)\Delta t \\ & - \lambda n\pi_{x_1}(t)\Delta t(1-\phi)(\alpha_h(\beta_{h_1}(t)+\beta_{h_2}(t)) + \alpha_y\beta_y(t)) + o(\Delta t). \end{aligned}$$

Subtracting $n\pi_{x_1}(t)$ from both sides, dividing by $n\Delta t$ and letting $\Delta t \to 0$ gives

$$\frac{d\pi_{x_1}}{dt} = \sigma(1-\alpha)\pi_{h_2} - \mu\pi_{x_1} - \lambda\pi_{x_1}(1-\phi)(\alpha_h(\beta_{h_1}+\beta_{h_2}) + \alpha_y\beta_y).$$

The number of acute h_1 infected IDUs at time $t+\Delta t$

= the number of acute h_1 infected IDUs at time t
+ the number of susceptible IDUs (both previously infected and previously uninfected) who develop acute h_1 HCV infection in $[t,\ t+\Delta t)$
− the number of acute h_1 IDUs who develop chronic HCV infection in $[t,\ t+\Delta t)$
− the number of acute h_1 IDUs who leave the population due to death or cessation of injecting drug use in $[t,\ t+\Delta t)$.

Thus we have

$$\begin{aligned} n\pi_{h_1}(t+\Delta t) = {} & n\pi_{h_1}(t) - (\mu+\sigma)n\Delta t\pi_{h_1}(t) \\ & + n\Delta t\lambda(1-\phi)(1-\delta)\left(1-\sum_i \pi_i\right)(\alpha_h(\beta_{h_1}(t)+\beta_{h_2}(t))+\alpha_y\beta_y(t)) \\ & - (\mu+\sigma)n\Delta t\pi_{h_1}(t) + o(\Delta t), \end{aligned}$$

where $\sum_i \pi_i = \pi_{h_1}(t)+\pi_{h_2}(t)+\pi_y(t)+\pi_z(t)$. Subtracting $n\pi_{h_1}(t)$ from both sides, dividing by $n\Delta t$ and letting $\Delta t \to 0$ gives

$$\begin{aligned} \frac{d\pi_{h_1}}{dt} = {} & \lambda(1-\phi)(1-\delta)(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y) \\ & - (\mu+\sigma)\pi_{h_1}. \end{aligned}$$

Similarly for acute h_2 infected IDUs we have

$$\begin{aligned} \frac{d\pi_{h_2}}{dt} = {} & \lambda(1-\phi)\delta(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y) \\ & - (\mu+\sigma)\pi_{h_2}. \end{aligned}$$

The number of chronic y infected IDUs at time $t+\Delta t$

= the number of chronically infected IDUs at time t

+ the number of acute h_1 infected IDUs that develop chronic HCV HCV infection in $[t,\ t{+}\Delta t)$

− the number of chronic cases that leave the population in $[t,\ t{+}\Delta t)$.

Thus we have

$$n\pi_y(t+\Delta t) = n\pi_y(t) + n(\pi_{h_1}(t)\sigma - \pi_y(t)\mu)\Delta t + o(\Delta t).$$

Subtracting $n\pi_y(t)$ from both sides, dividing by $n\Delta t$ then letting $\Delta t \to 0$ gives

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

Similarly for immume z IDUs we have

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

The number of acute h_1 needles and syringes at time $t{+}\Delta t$

= the number of acute h_1 infected needles and syringes at time t

+ the number of non acute h_1 needles and syringes used by acute h_1 infected IDUs in $[t,\ t{+}\Delta t)$

− the number of acute h_1 needles and syringes used by non acute h_1 IDUs in $[t,\ t{+}\Delta t)$

− the number of acute h_1 needles and syringes exchanged in $[t,\ t{+}\Delta t)$.

Thus we have

$$\begin{aligned} m\beta_{h_1}(t+\Delta t) =& m\beta_{h_1}(t) + m\Delta t\lambda\gamma\pi_{h_1}(t)\left(\beta_{h_2}(t) + \beta_y(t) + \left(1 - \sum_i \beta_i(t)\right)\right) \\ & - m\Delta t\lambda\gamma\beta_{h_1}(t)\left(\pi_{h_2}(t) + \pi_y(t) + \pi_z(t) + \left(1 - \sum_j \pi_i(t)\right)\right) \end{aligned}$$

$$-\tau m\beta_{h_1}(t)\Delta t + o(\Delta t),$$

where $\sum_i \beta_i(t) = \beta_{h_1}(t)+\beta_{h_2}(t)+\beta_y(t)$ and $\sum_j \pi_i(t) = \pi_{h_1}(t)+\pi_{h_2}(t)+\pi_y(t)+\pi_z(t)$. Subtracting $m\beta_{h_1}(t)$ from both sides, dividing by $m\Delta t$ then letting $\Delta t \to 0$ gives

$$\frac{d\beta_{h_1}}{dt} = \lambda\gamma(\pi_{h_1} - \beta_{h_1}) - \tau\beta_{h_1}.$$

Using a similar procedure we are able to obtain the following differential equations for acute h_2 and chronic y needles and syringes respectively:

$$\frac{d\beta_{h_2}}{dt} = \lambda\gamma(\pi_{h_2} - \beta_{h_2}) - \tau\beta_{h_2},$$
$$\frac{d\beta_y}{dt} = \lambda\gamma(\pi_y - \beta_y) - \tau\beta_y.$$

Hence the system of governing equations that describe the spread of HCV among IDUs is given by

$$\frac{d\pi_x}{dt} = \mu - \mu\pi_x - \lambda\pi_x(1-\phi)(\alpha_h(\beta_{h_1}+\beta_{h_2}) + \alpha_y\beta_y), \tag{3.1}$$
$$\frac{d\pi_{x_1}}{dt} = \sigma(1-\alpha)\pi_{h_2} - \mu\pi_{x_1} - \lambda\pi_{x_1}(1-\phi)(\alpha_h(\beta_{h_1}+\beta_{h_2}) + \alpha_y\beta_y), \tag{3.2}$$
$$\begin{aligned}\frac{d\pi_{h_1}}{dt} &= \lambda(1-\phi)(1-\delta)(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h(\beta_{h_1}+\beta_{h_2}) + \alpha_y\beta_y)\\ &\quad - (\mu+\sigma)\pi_{h_1},\end{aligned} \tag{3.3}$$
$$\begin{aligned}\frac{d\pi_{h_2}}{dt} &= \lambda(1-\phi)\delta(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h(\beta_{h_1}+\beta_{h_2}) + \alpha_y\beta_y)\\ &\quad - (\mu+\sigma)\pi_{h_2},\end{aligned} \tag{3.4}$$
$$\frac{d\pi_y}{dt} = \sigma\pi_{h_1} - \mu\pi_y, \tag{3.5}$$
$$\frac{d\pi_z}{dt} = \sigma\alpha\pi_{h_2} - \mu\pi_z, \tag{3.6}$$
$$\frac{d\beta_{h_1}}{dt} = \lambda\gamma(\pi_{h_1} - \beta_{h_1}) - \tau\beta_{h_1}, \tag{3.7}$$
$$\frac{d\beta_{h_2}}{dt} = \lambda\gamma(\pi_{h_2} - \beta_{h_2}) - \tau\beta_{h_2}, \tag{3.8}$$
$$\frac{d\beta_y}{dt} = \lambda\gamma(\pi_y - \beta_y) - \tau\beta_y, \tag{3.9}$$

with suitable initial conditions: $\pi_i(0) \geq 0$ and $\sum_i \pi_i = 1$ where $i = x, x_1, h_1, h_2, y, z$. $\beta_j(0) \geq 0$ and $\sum_j \beta_j \leq 1$ where $j = h_1, h_2, y$.

Equations (3.1)-(3.6) describe how the proportion of IDUs at each stage of HCV infection changes over time while equations (3.7)-(3.9) describe how the proportion of infectious needles and syringes changes over time in our model.

We have now derived the equations that govern the behaviour of our model for HCV spread. Before we analyse the behaviour of the model we derive an expression for the basic reproductive number R_0.

3.3 The basic reproductive number R_0

The basic reproductive number is a measure of the average number of secondary infections produced by a single infectious person (or needle) entering a population at DFE. Thus a secondary infection is a person infected through the use of an infectious needle and syringe, contaminated from use by the original infected IDU. R_0 is of critical importance in epidemiological models with the disease usually dying out when $R_0 < 1$ and an epidemic usually occurring when $R_0 > 1$. To derive the basic reproductive number we first consider a single newly infected IDU entering a disease free population containing only susceptible IDUs. The infection process can be broken into two stages:

1. The IDU passes the infection to uninfected needles and syringes.

2. The newly infected needles and syringes then infect susceptible IDUs.

We first derive the expected number of infectious needles generated from a single infectious IDU during their infectious lifetime. We then derive the expected number of infected IDUs resulting from these infectious needles. A single IDU injects at a rate λ and once infected with HCV moves into the acute h_1 class with probability $(1 - \delta)$ where they remain 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 IDU, once infected, can also move into the acute h_2 class with probability

δ where they remain for an average $1/(\mu+\sigma)$ time units. They then progress to either the immune class with probability $\sigma\alpha/(\mu+\sigma)$ where they remain for an average $1/\mu$ time units, or the x_1-susceptible class with probability $\sigma(1-\alpha)/(\mu+\sigma)$ where they again remain for an average $1/\mu$ time units, otherwise they leave the population. Hence on average an IDU generates

$$\frac{\lambda(1-\delta)}{\mu+\sigma}$$

acute h_1 infectious needles and syringes,

$$\frac{\lambda\delta}{\mu+\sigma}$$

acute h_2 infectious needles and syringes, and

$$\frac{\lambda\sigma(1-\delta)}{\mu(\mu+\sigma)}$$

chronic y infectious needles and syringes during their infectious lifetime. Now that we know how many of each type of infectious needle and syringe an IDU will generate during their infectious lifetime, we now wish to derive the expected number of HCV infected IDUs caused by each type of infectious needle and syringe until it is no longer infectious. Consider a single acute h_1 infectious needle and syringe which is used by IDUs at a rate λ. Define $E_{h_1}Y$ to be the number of IDUs infected by a single acute h_1 infectious needle and syringe, X_1 denote the event that the needle and syringe is made safe before the next injection and X_2 denote the event that the needle and syringe is still infectious at the time of the next injection, that is it is neither exchanged or cleaned. Therefore

$$E_{h_1}Y = E_{h_1}(Y|X_1)P(X_1) + E_{h_1}(Y|X_2)P(X_2).$$

If the needle and syringe is not infectious at the time of the next injection, then it will not infect any IDUs, so $E_{h_1}(Y|X_1) = 0$. The event X_2 corresponds to the needle remaining infectious at the time of the next injection. The probability of this depends on the fraction of needles and syringes available for sharing, given by $\lambda\gamma/(\lambda\gamma+\tau)$, and the probability the needle has not been successfully cleaned prior to use, given by $(1-\phi)$. Therefore, the probability of the event X_2 is

$\lambda\gamma(1-\phi)/(\lambda\gamma+\tau)$ and

$$E_{h_1}Y = \frac{\lambda\gamma(1-\phi)}{\lambda\gamma+\tau}E_{h_1}(Y|X_2).$$

We now examine the event $E_{h_1}(Y|X_2)$; a susceptible IDU injecting with an infectious needle. This event has only two possible outcomes: either the IDU is infected by the needle with probability α_h or remains susceptible with probability $1-\alpha_h$. Hence the expected number of IDUs infected by a single acute h_1 infectious needle is given by

$$E_{h_1}Y = \frac{(1-\phi)\alpha_h}{1+\hat{\tau}},$$

where $\hat{\tau} = \tau/\lambda\gamma$. We use a similar argument to derive the expected number of IDUs that are infected by acute h_2 and chronic y needles until they are not infectious and obtain

$$E_{h_2}Y = \frac{(1-\phi)\alpha_h}{1+\hat{\tau}},$$
$$E_yY = \frac{(1-\phi)\alpha_y}{1+\hat{\tau}}.$$

Multiplying the expected number of infections from each type of infectious needle and syringe with the expected number of needles and syringes that an IDU generates during their infectious lifetime gives us an expression for the total number of secondary infections caused by a single infectious IDU entering the disease free population. This gives

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

Hence the basic reproductive number is given by

$$R_0 = \frac{\lambda(1-\phi)}{\mu(\mu+\sigma)(1+\hat{\tau})}\left[\mu\alpha_h + \alpha_y\sigma(1-\delta)\right]. \tag{3.10}$$

We now examine the behaviour of our model analytically. In particular, we are interested in the conditions that allow HCV to die out or persist in the population.

3.4 Analytical results

In this section 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 will show that there are two equilibrium solutions; a zero and an unique non-zero solution. Stability analysis will show that the zero solution is globally stable when $R_0 < 1$ and unstable when $R_0 > 1$. Further analysis will show that the non-zero solution is locally stable when $R_0 > 1$ and the conditions necessary for the global stability of the non-zero equilibrium will be derived.

During the course of this analysis we assume that the probability of successful needle and syringe cleaning, ϕ, lies between zero and one but cannot take the value one. If we allow $\phi = 1$ then $R_0 = 0$ and no disease transmission will take place, $\phi = 0$ is allowed since this corresponds to a scenario where IDUs do not engage in cleaning practices prior to injecting. In addition, we assume that the remaining model parameters are strictly positive.

Theorem 3.1. *If $R_0 \leq 1$ the system of equations (3.1)-(3.9) has a unique equilibrium solution where HCV has died out in both IDUs and needles and syringes. If $R_0 > 1$ there is still the DFE, however there is also a unique endemic equilibrium point.*

Proof. Let π_i^* and β_j^* where $i = x,\ x_1,\ h_1,\ h_2,\ y,\ z$ and $j = h_1, h_2, y$ denote the endemic equilibrium proportions of IDUs and needles respectively. Setting $\frac{d}{dt} = 0$ in equations (3.1)-(3.9) and defining $\pi_{h_1}^* = (1-\delta)K$, which implies that $\pi_{h_2}^* = \delta K$ from (3.3) and (3.4) we find that

$$\begin{aligned} \frac{\pi_x^*}{\pi_{x_1}^*} = \frac{\mu}{\delta\sigma(1-\alpha)K}, \quad \pi_y^* = \frac{\sigma(1-\delta)K}{\mu}, \quad \pi_z^* = \frac{\sigma\alpha\delta K}{\mu}, \\ \beta_{h_1}^* = \frac{(1-\delta)K}{1+\hat{\tau}}, \quad \beta_{h_2}^* = \frac{\delta K}{1+\hat{\tau}}, \quad \beta_y^* = \frac{\sigma(1-\delta)K}{\mu(1+\hat{\tau})}, \end{aligned} \tag{3.11}$$

where $\hat{\tau} = \tau/\lambda\gamma$. Using equations (3.3)-(3.4) with $\frac{d}{dt} = 0$ we obtain

$$\begin{aligned} \pi_{h_1}^*(\mu+\sigma) &= \lambda(1-\phi)(1-\delta)(1-\pi_{h_1}^*-\pi_{h_2}^*-\pi_y^*-\pi_z^*)(\alpha_h(\beta_{h_1}^*+\beta_{h_2}^*)+\alpha_y\beta_y^*), \\ \pi_{h_2}^*(\mu+\sigma) &= \lambda(1-\phi)\delta(1-\pi_{h_1}^*-\pi_{h_2}^*-\pi_y^*-\pi_z^*)(\alpha_h(\beta_{h_1}^*+\beta_{h_2}^*)+\alpha_y\beta_y^*). \end{aligned}$$

Adding these together gives

$$K(\mu+\sigma) = \lambda(1-\phi)(1-K-\pi_y^*-\pi_z^*)(\alpha_h(\beta_{h_1}^*+\beta_{h_2}^*)+\alpha_y\beta_y^*),$$

where $K=(1-\delta)K+\delta K=\pi_{h_1}^*+\pi_{h_2}^*$. Using the expressions (3.11) for π_i^* and β_j^*, where $i=y,z$ and $j=h_1,h_2,y$ we find that $K(\mu+\sigma)$ is equal to

$$\lambda(1-\phi)\left(1-K-\frac{\sigma(1-\delta)K}{\mu}-\frac{\sigma\alpha\delta K}{\mu}\right)\left(\alpha_h\left(\frac{K}{1+\hat{\tau}}\right)+\frac{\alpha_y\sigma(1-\delta)K}{\mu(1+\hat{\tau})}\right).$$

Hence we have two cases for equilibrium. Either $K=0$ in which case we have the DFE solution or $K\neq 0$ in which case we can divide by K and solve the resulting equation for K. Using the expression for R_0 from equation (3.10) we find that

$$K=\frac{1}{P}\left(\frac{R_0-1}{R_0}\right), \tag{3.12}$$

where $P=1+\frac{\sigma}{\mu}(1-\delta(1-\alpha))$. This unique non-zero equilibrium point is strictly positive if and only if $R_0>1$. The equilibrium equations then give unique positive values of π_x^* and $\pi_{x_1}^*$ and by adding the equilibrium versions of (3.1)-(3.6) and (3.7)-(3.9) it is straightforward to show that $\pi_x^*+\pi_{x_1}^*+\pi_{h_1}^*+\pi_{h_2}^*+\pi_y^*+\pi_z^*=1$ and $\beta_{h_1}^*+\beta_{h_2}^*+\beta_y^*<1$. □

We now turn our attention to 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 all IDUs and needles and syringes.

Theorem 3.2. *If $R_0\leq 1$ HCV will be eliminated in all IDUs and needles and syringes.*

Proof. This result is proved in several stages. We write $\pi_{h_1}^\infty$ for $\limsup_{t\to\infty}\pi_{h_1}(t)$, with similar definitions for the other π_i^∞ and β_j^∞ for $i=h_2$, y, z and $j=h_1$, h_2, y. We first prove several results that give upper bounds on the limit suprema of each IDU and needle class in terms of either $\pi_{h_1}^\infty$ or $\pi_{h_2}^\infty$. Using equations (3.3) and (3.4) we are able to find a relationship between $\pi_{h_1}^\infty$ and $\pi_{h_2}^\infty$, thus allowing us to express our earlier results in terms of a single limit supremum. We then show if $R_0\leq 1$ this limit supremum must be equal to zero. Applying this result will

complete the proof.

Lemma 3.1. $\pi_y^\infty \leq \dfrac{\sigma \pi_{h_1}^\infty}{\mu}$.

Proof. From equation (3.5) we have, noting that $\pi_{h_1} \leq \pi_{h_1}^\infty + \epsilon$, $\forall t \geq t_1(\epsilon)$

$$\begin{aligned}\frac{d}{dt}\left[\pi_y \exp(\mu t)\right] &= \pi_{h_1}\sigma\exp(\mu t), \\ &\leq (\pi_{h_1}^\infty + \epsilon)\sigma\exp(\mu t), \quad \forall t \geq t_1(\epsilon),\ \epsilon > 0.\end{aligned}$$

Integrating over $[t_1(\epsilon), t]$ gives

$$\begin{aligned}\pi_y(t) &\leq \pi_y(t_1(\epsilon))\exp[(-\mu)(t - t_1(\epsilon))] + (\pi_{h_1}^\infty + \epsilon)\sigma\left[\frac{1 - \exp[(-\mu)(t - t_1(\epsilon))]}{\mu}\right], \\ &\leq \epsilon + \frac{(\pi_{h_1}^\infty + \epsilon)\sigma}{\mu} \quad \forall t \geq t_2(\epsilon), \text{ for some } t_2(\epsilon) > t_1(\epsilon) \text{ sufficiently large.}\end{aligned}$$

Taking the limsup and letting $t \to \infty$ we have

$$\pi_y^\infty \leq \frac{\sigma \pi_{h_1}^\infty}{\mu} + \epsilon_1, \qquad \text{where } \epsilon_1 = \epsilon\left(\frac{\mu + \sigma}{\mu}\right).$$

Suppose that $\pi_y^\infty > \dfrac{\sigma \pi_{h_1}^\infty}{\mu}$. Since $\epsilon_1 > 0$ is arbitrary we can choose $\epsilon_1 = \dfrac{1}{2}\left(\pi_y^\infty - \dfrac{\sigma}{\mu}\pi_{h_1}^\infty\right)$ which provides a contradiction and hence the result follows. □

Corollary 3.1. $\pi_z^\infty \leq \dfrac{\sigma\alpha\pi_{h_2}^\infty}{\mu}$.

Proof. Using equation (3.6) and the method used in the proof of Lemma 3.1 the result follows. □

Using the same method and equations (3.7)-(3.9) it is straightforward to show that

$$\beta_{h_1}^\infty \leq \frac{\pi_{h_1}^\infty}{1 + \hat{\tau}}, \quad \beta_{h_2}^\infty \leq \frac{\pi_{h_2}^\infty}{1 + \hat{\tau}} \text{ and } \beta_y^\infty \leq \frac{\pi_y^\infty}{1 + \hat{\tau}}. \tag{3.13}$$

Note that we can rewrite the third inequality in (3.13) in terms of $\pi^{\infty}_{h_1}$ by using Lemma 3.1. We now use equations (3.3) and (3.4) to find a relationship between $\pi^{\infty}_{h_1}$ and $\pi^{\infty}_{h_2}$.

Lemma 3.2. $(1-\delta)\pi^{\infty}_{h_2} = \delta\pi^{\infty}_{h_1}$.

Proof. We begin by proving that $\delta\pi^{\infty}_{h_1} \leq (1-\delta)\pi^{\infty}_{h_2}$. Dividing equation (3.3) by $(1-\delta)$ and equation (3.4) by δ then subtracting the results gives

$$\frac{d}{dt}\left(\frac{\pi_{h_1}}{1-\delta} - \frac{\pi_{h_2}}{\delta}\right) = -(\mu+\sigma)\left(\frac{\pi_{h_1}}{1-\delta} - \frac{\pi_{h_2}}{\delta}\right). \tag{3.14}$$

The general solution to this equation shows that

$$\delta\pi_{h_1} - (1-\delta)\pi_{h_2} \to 0 \text{ as } t \to \infty. \tag{3.15}$$

Hence given $\epsilon > 0$ there exists t_3 such that for $t \geq t_3$, $\delta\pi_{h_1} \leq (1-\delta)\pi_{h_2} + (\epsilon/2)$. In addition, there exists $t_4 \geq t_3$ such that for $t \geq t_4$

$$(1-\delta)\pi_{h_2} \leq (1-\delta)\left(\pi^{\infty}_{h_2} + \frac{\epsilon}{2(1-\delta)}\right).$$

Therefore for $t \geq t_4$ we have $\delta\pi_{h_1} \leq (1-\delta)\pi^{\infty}_{h_2} + \epsilon$. So

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

Since ϵ is arbitrary, we deduce that $\delta\pi^{\infty}_{h_1} \leq (1-\delta)\pi^{\infty}_{h_2}$. We can use a similar proof to show the reverse inequality and hence the result follows. □

Define $\pi_h = \pi_{h_1} + \pi_{h_2}$. Suppose that $\pi^{\infty}_{h_1} > 0$. Using (3.15) it is straightforward to show that $\pi^{\infty}_h = \pi^{\infty}_{h_1}/(1-\delta) = \pi^{\infty}_{h_2}/\delta$. We can use Lemma 3.2 to write the inequalities in Lemma 3.1, Corollary 3.1 and (3.13) in terms of π^{∞}_h to obtain:

$$\pi^{\infty}_y \leq \frac{\sigma(1-\delta)\pi^{\infty}_h}{\mu}, \tag{3.16}$$

$$\pi^{\infty}_z \leq \frac{\sigma\alpha\delta\pi^{\infty}_h}{\mu}, \tag{3.17}$$

$$\beta^{\infty}_{h_1} \leq \frac{(1-\delta)\pi^{\infty}_h}{1+\hat{\tau}}, \tag{3.18}$$

$$\beta_{h_2}^{\infty} \leq \frac{\delta \pi_h^{\infty}}{1+\hat{\tau}}, \tag{3.19}$$

$$\beta_y^{\infty} \leq \frac{\sigma(1-\delta)\pi_h^{\infty}}{\mu(1+\hat{\tau})}. \tag{3.20}$$

Adding equations (3.3) and (3.4) together we have

$$\begin{aligned}
\frac{d\pi_h}{dt} &= \lambda(1-\phi)(1-\pi_h-\pi_y-\pi_z)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y)-(\mu+\sigma)\pi_h, \\
&\leq \lambda(1-\phi)(1-\pi_h)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y)-(\mu+\sigma)\pi_h, \\
&\leq \lambda(1-\phi)(1-\pi_h)(\alpha_h(\beta_{h_1}^{\infty}+\beta_{h_2}^{\infty})+\alpha_y\beta_y^{\infty}+\epsilon)-(\mu+\sigma)\pi_h,
\end{aligned}$$

$$\text{for } \epsilon > 0, \quad t \geq t_5(\epsilon).$$

Substituting in the upper bounds for $\beta_{h_1}^{\infty}$, $\beta_{h_2}^{\infty}$ and β_y^{∞} given by inequalities (3.18)-(3.20) yields

$$\begin{aligned}
\frac{d\pi_h}{dt} &\leq \lambda(1-\phi)(1-\pi_h)\left(\alpha_h\left(\frac{(1-\delta)\pi_h^{\infty}}{1+\hat{\tau}}+\frac{\delta\pi_h^{\infty}}{1+\hat{\tau}}\right)+\alpha_y\frac{\sigma(1-\delta)\pi_h^{\infty}}{\mu(1+\hat{\tau})}+\epsilon\right) \\
&\quad -(\mu+\sigma)\pi_h, \\
&\leq (\mu+\sigma)\left[(1-\pi_h)\frac{\lambda(1-\phi)}{\mu(\mu+\sigma)(1+\hat{\tau})}(\mu\alpha_h+\sigma\alpha_y(1-\delta))\pi_h^{\infty}+\epsilon_2-\pi_h\right],
\end{aligned}$$

where $\epsilon_2 = \dfrac{\epsilon\lambda(1-\phi)}{(\mu+\sigma)}$. Using equation (3.10) we obtain

$$\frac{d\pi_h}{dt} \leq (\mu+\sigma)[(R_0+\epsilon_3)\pi_h^{\infty}-(R_0\pi_h^{\infty}+1)\pi_h], \quad \text{where } \epsilon_3 = \frac{\epsilon\lambda(1-\phi)}{(\mu+\sigma)\pi_h^{\infty}}.$$

Hence for all $t \geq t_5(\epsilon)$

$$\begin{aligned}
&\frac{d}{dt}\left[\pi_h(t)\exp[(\mu+\sigma)(1+R_0\pi_h^{\infty})t]\right] \\
&\qquad\qquad \leq (\mu+\sigma)(R_0+\epsilon_3)\pi_h^{\infty}\exp\left[(\mu+\sigma)(1+R_0\pi_h^{\infty})t\right].
\end{aligned}$$

Integrating over $[t_5(\epsilon), t]$ and using a similar method to that used in the proof of Lemma 3.1 we have that

$$\pi_h^{\infty} \leq \frac{\pi_h^{\infty}R_0}{(1+R_0\pi_h^{\infty})}+\epsilon_5, \quad \text{where } \epsilon_5 = \epsilon_4+\frac{\epsilon_3\pi_h^{\infty}}{(1+R_0\pi_h^{\infty})}$$

and ϵ_4 is an arbitrarily small positive constant. When $0 \leq R_0 \leq 1$ we have that

$$\pi_h^\infty - \frac{\pi_h^\infty R_0}{(1 + R_0 \pi_h^\infty)} > 0.$$

Since $\epsilon_5 > 0$ is arbitrary we can choose

$$\epsilon_5 = \frac{1}{2}\left(\pi_h^\infty - \frac{R_0 \pi_h^\infty}{1 + R_0 \pi_h^\infty}\right).$$

This leads to a contradiction and hence we deduce that $\pi_h^\infty = 0$ provided that $0 \leq R_0 \leq 1$. $\pi_h^\infty = 0$ implies that $\pi_{h_1}^\infty = \pi_{h_2}^\infty = \pi_y^\infty = \pi_z^\infty = \beta_{h_1}^\infty = \beta_{h_2}^\infty = \beta_y^\infty = 0$ using (3.16)-(3.20) and the comments immediately before these equations. Therefore, we must have $\lim_{t\to\infty} \pi_{h_1}(t) = \lim_{t\to\infty} \pi_{h_2}(t) = \lim_{t\to\infty} \pi_y(t) = \lim_{t\to\infty} \pi_z(t) = \lim_{t\to\infty} \beta_{h_1}(t) = \lim_{t\to\infty} \beta_{h_2}(t) = \lim_{t\to\infty} \beta_y(t) = 0$. It is then straightforward to show that $\lim_{t\to\infty} \pi_{x_1}(t) = 0$. This completes the proof of the global stability of the DFE when $0 \leq R_0 \leq 1$. □

We have examined the behaviour of our transmission model when $0 \leq R_0 \leq 1$ and shown that this condition is necessary for HCV elimination among IDUs. We now turn our attention to what happens when $R_0 > 1$. We will first prove that under this condition the DFE is unstable. Further analysis will show that when $R_0 > 1$ HCV will remain persistent in the population and the endemic equilibrium is locally stable.

Theorem 3.3. *If $R_0 > 1$ the DFE is unstable.*

Proof. We consider the linearised system of equations (3.1)-(3.9) which are evaluated at the DFE. When linearising about the DFE we have that $\pi_x = 1 + \pi_x^{'}, \pi_{x_1} = 0 + \pi_{x_1}^{'}, \pi_{h_1} = 0 + \pi_{h_1}^{'}, \pi_{h_2} = 0 + \pi_{h_2}^{'}, \pi_y = 0 + \pi_y^{'}, \pi_z = 0 + \pi_z^{'}, \beta_{h_1} = 0 + \beta_{h_1}^{'}, \beta_{h_2} = 0 + \beta_{h_2}^{'}$ and $\beta_y = 0 + \beta_y^{'}$, where the prime terms denote small perturbations about the equilibrium point. Substituting these terms into equations (3.1)-(3.9) and linearising then dropping the prime notation for convenience gives

$$\frac{d\pi_x}{dt} = -\mu\pi_x - \lambda(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y),$$
$$\frac{d\pi_{x_1}}{dt} = \sigma(1-\alpha)\pi_{h_2} - \mu\pi_{x_1},$$

$$
\begin{aligned}
\frac{d\pi_{h_1}}{dt} &= \lambda(1-\phi)(1-\delta)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y)-(\mu+\sigma)\pi_{h_1},\\
\frac{d\pi_{h_2}}{dt} &= \lambda(1-\phi)\delta(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y)-(\mu+\sigma)\pi_{h_2},\\
\frac{d\pi_y}{dt} &= \sigma\pi_{h_1}-\mu\pi_y,\\
\frac{d\pi_z}{dt} &= \sigma\alpha\pi_{h_2}-\mu\pi_z,\\
\frac{d\beta_{h_1}}{dt} &= \lambda\gamma(\pi_{h_1}-\beta_{h_1})-\tau\beta_{h_1},\\
\frac{d\beta_{h_2}}{dt} &= \lambda\gamma(\pi_{h_2}-\beta_{h_2})-\tau\beta_{h_2},\\
\frac{d\beta_y}{dt} &= \lambda\gamma(\pi_y-\beta_y)-\tau\beta_y.
\end{aligned}
$$

This system describes the population dynamics in the neighbourhood of the equilibrium point and can be expressed in the matrix form $d\mathbf{x}/dt = \mathbf{J}\mathbf{x}$, where $\mathbf{x}^T = (\pi_x, \pi_{x_1}, \pi_{h_1}, \pi_{h_2}, \pi_y, \pi_z, \beta_{h_1}, \beta_{h_2}, \beta_y)$ and $\mathbf{J}$ is given by

$$
\begin{bmatrix}
-\mu & 0 & 0 & 0 & 0 & 0 & -\lambda(1-\phi)\alpha_h & -\lambda(1-\phi)\alpha_h & -\lambda(1-\phi)\alpha_y\\
0 & -\mu & 0 & \sigma(1-\alpha) & 0 & 0 & 0 & 0 & 0\\
0 & 0 & -(\mu+\sigma) & 0 & 0 & 0 & \lambda(1-\phi)(1-\delta)\alpha_h & \lambda(1-\phi)(1-\delta)\alpha_h & \lambda(1-\phi)(1-\delta)\alpha_y\\
0 & 0 & 0 & -(\mu+\sigma) & 0 & 0 & \lambda(1-\phi)\delta\alpha_h & \lambda(1-\phi)\delta\alpha_h & \lambda(1-\phi)\delta\alpha_y\\
0 & 0 & \sigma & 0 & -\mu & 0 & 0 & 0 & 0\\
0 & 0 & 0 & \sigma\alpha & 0 & -\mu & 0 & 0 & 0\\
0 & 0 & \lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau) & 0 & 0\\
0 & 0 & 0 & \lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau) & 0\\
0 & 0 & 0 & 0 & \lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau)
\end{bmatrix}.
$$

We wish to look at the neighbourhood stability of this matrix which is characterised by its eigenvalues. For the DFE to be unstable we wish to show that at least one eigenvalue has a strictly positive real part. The characteristic equation for this matrix is a ninth order polynomial in ω and the Routh-Hurwitz conditions tell us that for instability it is sufficient to show that the constant term $a_9 < 0$ (assuming that the leading term is ω^9). It is straightforward to show that

$$
\begin{aligned}
a_9 &= \mu^4(\mu+\sigma)^2(\lambda\gamma+\tau)^3\left[1-\left(\frac{\lambda(1-\phi)\lambda\gamma\alpha_h}{(\lambda\gamma+\tau)(\mu+\sigma)}+\frac{\lambda(1-\phi)(1-\delta)\sigma\lambda\gamma\alpha_y}{\mu(\mu+\sigma)(\lambda\gamma+\tau)}\right)\right],\\
&= \mu^4(\mu+\sigma)^2(\lambda\gamma+\tau)^3[1-R_0].
\end{aligned}
$$

It is clear that this term is negative when $R_0 > 1$ and the result follows. □

We are now going to examine the persistence of HCV when $R_0 > 1$. In this model we have that π_{h_1} and π_{h_2} are the dominant terms and hence if they become small then so do the other terms. We are going to use Theorem 3.3 to show that if $R_0 > 1$ these terms cannot become arbitrarily small and hence can be bounded away from the origin. As with Theorem 3.2 we are going to prove this in several stages. Hence we need the following lemma. Let $\pi_{h_1,\infty} = \liminf_{t\to\infty}\pi_{h_1}(t)$, with similar definitions for the other variables.

Lemma 3.3. *If* $\pi_{y,\infty} = liminf_{t\to\infty}\pi_y(t)$ *then*

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

Proof. From equation (3.5) we have, noting that $\pi_{h_1} \geq \pi_{h_1,\infty} - \epsilon, \forall t \geq t_1(\epsilon)$

$$\begin{aligned}\frac{d}{dt}\left[\pi_y \exp(\mu t)\right] &= \sigma\pi_{h_1}\exp(\mu t),\\ &\geq (\pi_{h_1,\infty} - \epsilon)\sigma\exp(\mu t), \quad \forall t \geq t_1(\epsilon),\ \epsilon > 0.\end{aligned}$$

Integrating over $[t_1(\epsilon), t]$ gives

$$\begin{aligned}\pi_y(t) &\geq \pi_y(t_1(\epsilon))\exp[(-\mu)(t - t_1(\epsilon))] + (\pi_{h_1,\infty} - \epsilon)\sigma\left[\frac{1 - \exp[(-\mu)(t - t_1(\epsilon))]}{\mu}\right],\\ &\geq \frac{(\pi_{h_1,\infty} - \epsilon)\sigma}{\mu} - \epsilon, \quad \forall t \geq t_2(\epsilon), \text{ for some } t_2(\epsilon) > t_1(\epsilon) \text{ sufficiently large.}\end{aligned}$$

Taking the liminf and letting $t \to \infty$ we have

$$\pi_{y,\infty} \geq \frac{\sigma\pi_{h_1,\infty}}{\mu} - \epsilon_1, \qquad \text{where } \epsilon_1 = \frac{\epsilon(\mu + \sigma)}{\mu}.$$

Suppose that $\frac{\sigma\pi_{h_1,\infty}}{\mu} > \pi_{y,\infty}$. Since $\epsilon_1 > 0$ is arbitrary we can choose $\epsilon_1 = \frac{1}{2}\left[\frac{\sigma\pi_{h_1,\infty}}{\mu} - \pi_{y,\infty}\right]$ to obtain a contradiction and complete the proof. □

Lemma 3.4. *If* $\pi_{z,\infty} = liminf_{t\to\infty}\pi_z(t)$ *then*

$$\pi_{z,\infty} \geq \frac{\sigma\alpha\pi_{h_2,\infty}}{\mu}.$$

Proof. Using equation (3.6) and the method used in the proof of Lemma 3.3 the result follows. □

Using the same method and equations (3.7)-(3.9) it is straightforward to show that

$$\beta_{h_1,\infty} \geq \frac{\pi_{h_1,\infty}}{1+\hat{\tau}},\ \beta_{h_2,\infty} \geq \frac{\pi_{h_2,\infty}}{1+\hat{\tau}} \text{ and } \beta_{y,\infty} \geq \frac{\sigma\pi_{h_1,\infty}}{\mu(1+\hat{\tau})}. \tag{3.21}$$

In order to prove Theorem 3.2 we needed to find a relationship between $\pi^{\infty}_{h_1}$ and $\pi^{\infty}_{h_2}$. In a similar way, we need to find a relationship between $\pi_{h_1,\infty}$ and $\pi_{h_2,\infty}$.

Lemma 3.5. $(1-\delta)\pi_{h_2,\infty} = \delta\pi_{h_1,\infty}$.

Proof. We begin by proving that $\delta\pi_{h_1,\infty} \geq (1-\delta)\pi_{h_2,\infty}$. By the proof of Lemma 3.2

$$\delta\pi_{h_1} - (1-\delta)\pi_{h_2} \to 0 \text{ as } t \to \infty.$$

Hence given any $\epsilon > 0$ there exists $t_3 > 0$ such that for $t \geq t_3$, $\delta\pi_{h_1} \geq (1-\delta)\pi_{h_2} - (\epsilon/2)$. In addition, there exists $t_4 > t_3$ such that for $t \geq t_4$

$$(1-\delta)\pi_{h_2} \geq (1-\delta)\left(\pi_{h_2,\infty} - \frac{\epsilon}{2(1-\delta)}\right).$$

Therefore for $t \geq t_4$ we have $\delta\pi_{h_1} \geq (1-\delta)\pi_{h_2,\infty} - \epsilon$. So

$$\delta\pi_{h_1,\infty} = \liminf_{t\to\infty} \delta\pi_{h_1} \geq (1-\delta)\pi_{h_2,\infty} - \epsilon.$$

Since ϵ is arbitrary, we deduce that $\delta\pi_{h_1,\infty} \geq (1-\delta)\pi_{h_2,\infty}$. We can use a similar proof to show the reverse inequality and hence the result follows. □

From this we deduce that it is sufficient to show that $\pi_{h_1,\infty} > 0$ in order to bound trajectories away from zero.

Lemma 3.6. *Provided that at least one of* $\pi_{h_1}(0)$, $\pi_{h_2}(0)$, $\pi_y(0)$, $\beta_{h_1}(0)$, $\beta_{h_2}(0)$ *and* $\beta_y(0)$ *is strictly positive then* $\pi_{h_1}(\Delta t)$, $\pi_{h_2}(\Delta t)$, $\pi_y(\Delta t)$, $\pi_z(\Delta t)$, $\beta_{h_1}(\Delta t)$, $\beta_{h_2}(\Delta t)$ *and* $\beta_y(\Delta t)$ *are all greater than zero for small* $\Delta t > 0$.

Proof. We need to consider four initial conditions:

1. $\beta(0) = 0$, $\pi(0) > 0$,
2. $\beta(0) > 0$, $\pi(0) = 0$,
3. $\beta(0) > 0$, $\pi(0) > 0$, $1 - \pi^+(0) > 0$,
4. $\beta(0) > 0$, $\pi(0) > 0$, $1 - \pi^+(0) = 0$,

where $\pi = \sum_i \pi_i$, $\beta = \sum_i \beta_i$, for $i = h_1, h_2, y$ and $\pi^+ = \sum_j \pi_j$, for $j = h_1, h_2, y, z$. Define $\psi = 1 - \pi^+$.

Case 1. Using Taylor series expansions about $t = 0$ and the appropriate model equations gives

$\pi(\Delta t) = \pi(0) - (\mu + \sigma)(\pi_{h_1}(0) + \pi_{h_2}(0))\Delta t + (\sigma\pi_{h_1}(0) - \mu\pi_y(0))\Delta t + o(\Delta t)$,

$\beta(\Delta t) = \lambda\gamma\pi(0)\Delta t + o(\Delta t)$.

If $\psi(0) > 0$ then clearly $\psi(\Delta t) > 0$ for Δt small and positive. If $\psi(0) = 0$ then as

$$\frac{d\psi}{dt} = -\lambda(1 - \phi)\psi A + \mu(1 - \psi) + \sigma(1 - \alpha)\pi_{h_2}$$

where $A = \alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y$, we have $\psi(\Delta t) \geq \mu\Delta t + o(\Delta t) > 0$ if Δt is small enough. By choosing $\Delta t > 0$ small enough and starting at $t = \Delta t$ rather than $t = 0$ we can assume that $\pi(0) > 0$, $\psi(0) > 0$ and $\beta(0) > 0$ if necessary. If $\pi_{h_1}(0) = 0$ then

$$\pi_{h_1}(\Delta t) = \lambda\psi(0)(1 - \delta)(1 - \phi)A(0)\Delta t + o(\Delta t) > 0$$

if $\Delta t > 0$ is small enough. So starting at $t = \Delta t$ if necessary we can assume that $\pi_{h_1}(0) > 0$. We may similarly assume that $\pi_{h_2}(0), \pi_y(0), \pi_z(0), \beta_{h_1}(0), \beta_{h_2}(0)$ and $\pi_z(0) > 0$. The result follows.

Case 2. Suppose that $\pi(0) = 0$ and $\beta(0) > 0$. If $\pi_z(0) = 1$ then $\pi_z(\Delta t) = 1 - \mu\Delta t + o(\Delta t) < 1$ for small Δt. Hence we can assume without loss of generality that $\pi_z(0) < 1$. Using the same method as in the previous case we find that, for small Δt,

$$\pi(\Delta t) = \lambda(1 - \phi)(1 - \pi_z(0))A(0)\Delta t + o(\Delta t) > 0,$$
$$\beta(\Delta t) = \beta(0) - \lambda\gamma\beta(0)\Delta t - \beta(0)\tau\Delta t + o(\Delta t) > 0,$$

$$\psi(\Delta t) = 1 - \pi_z(0) - \lambda(1-\phi)(1-\pi^+)A(0)\Delta t + \pi_{h_2}(0)\sigma(1-\alpha)\Delta t$$
$$+ \mu(1-\psi(0))\Delta t + o(\Delta t) > 0.$$

By choosing Δt small enough and starting at $t = \Delta t$ we can assume if necessary $\pi(0)$, $\psi(0)$ and $\beta(0) > 0$. The proof proceeds as in Case 1.

Case 3. Suppose that $\beta(0) > 0$, $\pi(0) > 0$, $1 - \pi^+(0) > 0$. The proof again proceeds as in Case 1.

Case 4. Suppose that $\beta(0) > 0$, $\pi(0) > 0$, $1 - \pi^+(0) = 0$. This implies that $\pi^+(0) = 1$. We again show that similarly to the above that without loss of generality we can assume that $\pi(0)$, $\beta(0)$ and $\psi(0) > 0$ and the required result follows. This completes our proof of Lemma 3.6. □

Theorem 3.4. *If $R_0 > 1$ and either $\pi(0)$ or $\beta(0)$ is strictly positive then there exists $\epsilon > 0$ and $\eta > 0$ such that for $t \geq \eta$*

$$\pi_{h_1} \geq \epsilon\pi^*_{h_1}, \pi_{h_2} \geq \epsilon\pi^*_{h_2}, \pi_y \geq \epsilon\pi^*_y, \pi_z \geq \epsilon\pi^*_z, \beta_{h_1} \geq \epsilon\beta^*_{h_1}, \beta_{h_2} \geq \epsilon\beta^*_{h_2}, \beta_y \geq \epsilon\beta^*_y.$$

Here ϵ is a fixed positive small quantity independent of the initial conditions.

Proof. Suppose that ϵ is fixed and small. We shall define ϵ more precisely later (3.22). We have either $\pi_{h_1,\infty} \geq \frac{1}{2}\epsilon\pi^*_{h_1}$ or $\pi_{h_1,\infty} < \frac{1}{2}\epsilon\pi^*_{h_1}$. Suppose first that $\pi_{h_1,\infty} \geq \frac{1}{2}\epsilon\pi^*_{h_1}$. By the definition of $\pi_{h_1,\infty}$ there exists T_1 such that for all $t \geq T_1$, $\pi_{h_1} \geq \frac{1}{4}\epsilon\pi^*_{h_1}$. Then using Lemma 3.5 we find

$$\pi_{h_2,\infty} = \frac{\delta}{(1-\delta)}\pi_{h_1,\infty} \geq \frac{1}{2}\epsilon\frac{\delta}{(1-\delta)}\pi^*_{h_1} = \frac{1}{2}\epsilon\pi^*_{h_2}.$$

Arguing similarly to the above there exists T_2 such that for $t \geq T_2$ $\pi_{h_2} \geq \frac{1}{4}\epsilon\pi^*_{h_2}$. Using Lemmas 3.3 and 3.4 and inequalities (3.21) and arguing similarly to the above we find that there exists a T_3 such that for all $t \geq T_3$, $\pi_y \geq \frac{1}{4}\epsilon\pi^*_y$, $\pi_z \geq \frac{1}{4}\epsilon\pi^*_z$, $\beta_{h_1} \geq \frac{1}{4}\epsilon\beta^*_{h_1}$, $\beta_{h_2} \geq \frac{1}{4}\epsilon\beta^*_{h_2}$ and $\beta_y \geq \frac{1}{4}\epsilon\beta^*_y$. Hence Theorem 3.4 is true in this case.

On the other hand, if $\pi_{h_1,\infty} < \frac{1}{2}\epsilon\pi^*_{h_1}$, then Lemma 3.6 shows that $\pi_{h_1}(\Delta t) > 0$. If $\pi_{h_1,\infty} < \frac{1}{2}\epsilon\pi^*_{h_1}$ then there exists $\xi \geq \Delta t$ where $\pi_{h_1}(\xi) < \frac{1}{2}\epsilon\pi^*_{h_1}$. We define $t_0 = \inf\{\xi \geq \Delta t, \pi_{h_1}(\xi) < \frac{1}{2}\epsilon\pi^*_{h_1}\}$ to be the first time after $t = \Delta t$ where π_{h_1} starts to go below $\frac{1}{2}\epsilon\pi^*_{h_1}$, and $t_1 = \inf\{\xi \geq t_0, \pi_{h_1}(\xi) > \frac{1}{2}\epsilon\pi^*_{h_1}\}$ to be the first time

after $t = t_0$ where π_{h_1} rises above $\frac{1}{2}\epsilon\pi^*_{h_1}$. If $\pi_{h_1}(\Delta t) \geq \frac{1}{2}\epsilon\pi^*_{h_1}$ then by the definition of t_0 we have $\pi_{h_1}(t_0 + \nu) < \frac{1}{2}\epsilon\pi^*_{h_1}$ for some ν small and positive. Hence $t_1 > t_0$ and by continuity $\pi_{h_1}(t_0) = \frac{1}{2}\epsilon\pi^*_{h_1} = \pi_{h_1}(t_1)$ and so $\pi_{h_1} \leq \frac{1}{2}\epsilon\pi^*_{h_1}$ in (t_0, t_1) and $\pi_{h_1} > \frac{1}{2}\epsilon\pi^*_{h_1}$ just after t_1. We shall now show that if π_{h_1} becomes small then all other variables must also become small.

Lemma 3.7. *If $\Delta > 0$ is small and positive then there exists a time $\overline{T}_1 > 0$ such that if $t_0 + \overline{T}_1 < t_1$, then for all $t \in [t_0 + \overline{T}_1, t_1]$, $0 < \pi_y < (\frac{1}{2} + \Delta)\epsilon\pi^*_y$, where $\overline{T}_1$ depends only on the model parameters, Δ and ϵ.*

Proof. We know that $\pi_{h_1} \leq \frac{1}{2}\epsilon\pi^*_{h_1}$ in $[t_0, t_1]$, hence using equation (3.5) we have

$$\begin{aligned}\frac{d}{dt}[\pi_y \exp(\mu t)] =& \sigma\pi_{h_1}\exp[\mu t],\\ \leq& \frac{1}{2}\epsilon\pi^*_{h_1}\sigma\exp[\mu t].\end{aligned}$$

Integrating over $[t_0, t]$ gives

$$\begin{aligned}\pi_y(t) &\leq \pi_y(t_0)\exp[(-\mu)(t - t_0)] + \frac{1}{2}\epsilon\pi^*_{h_1}\frac{\sigma}{\mu},\\ &\leq \exp[(-\mu)(t - t_0)] + \frac{1}{2}\epsilon\pi^*_{h_1}\frac{\sigma}{\mu},\\ &= \exp[-\mu(t - t_0)] + \frac{1}{2}\epsilon\pi^*_y.\end{aligned}$$

Hence, provided that t is sufficiently large, say $t \geq t_0 + \overline{T}_1$, then the result holds. □

In Lemma 3.7 we have shown that if π_{h_1} becomes small then this causes π_y to become small. We shall now prove similar results for $\pi_{h_2}, \pi_z, \beta_{h_1}, \beta_{h_2}$, and β_y.

Lemma 3.8. *There exists a time $\overline{T}_2 > 0$, dependent only on the model parameters, Δ and ϵ such that for $t \in (t_0 + \overline{T}_2, t_1)$, $0 < \pi_{h_2} < (\frac{1}{2} + \Delta)\epsilon\pi^*_{h_2}$.*

Proof. Define $x = \dfrac{\pi_{h_1}}{(1-\delta)} - \dfrac{\pi_{h_2}}{\delta}$. From equation (3.14) we have

$$|x(t)| = \left|\frac{\pi_{h_1}}{1-\delta} - \frac{\pi_{h_2}}{\delta}\right|,$$

$$
\begin{aligned}
&= \left| \frac{\pi_{h_1}(0)}{1-\delta} - \frac{\pi_{h_2}(0)}{\delta} \right| e^{-(\mu+\sigma)t}, \\
&\leq \left| \frac{\pi_{h_1}(0)}{1-\delta} + \frac{\pi_{h_2}(0)}{\delta} \right| e^{-(\mu+\sigma)t}, \\
&\leq \frac{e^{-(\mu+\sigma)t}}{\delta(1-\delta)}, \qquad \text{as } \pi_{h_1}(0),\, \pi_{h_2}(0) \leq 1.
\end{aligned}
$$

Using the triangle inequality we find that

$$
\pi_{h_2} \leq \frac{\delta \pi_{h_1}}{1-\delta} + \frac{e^{-(\mu+\sigma)t}}{1-\delta}.
$$

Hence in the interval $[t_0, t_1]$

$$
\pi_{h_2} \leq \frac{1}{2}\epsilon \pi^*_{h_2} + \frac{e^{-(\mu+\sigma)t}}{1-\delta}.
$$

Therefore, provided that t is sufficiently large the result follows. □

Lemma 3.9. *There exists a time $\overline{T}_3 > 0$, dependent only on the model parameters, Δ and ϵ such that for $t \in (t_0 + \overline{T}_2 + \overline{T}_3, t_1)$, $0 < \pi_z < (\frac{1}{2} + 2\Delta)\epsilon\pi^*_z$.*

Proof. Using equation (3.6) and Lemma 3.8 we have in $(t_0 + \overline{T}_2, t_1)$

$$
\begin{aligned}
\frac{d}{dt}[\pi_z \exp(\mu t)] &= \sigma\alpha\pi_{h_2}\exp(\mu t), \\
&\leq \left(\frac{1}{2} + \Delta\right)\sigma\alpha\epsilon\pi^*_{h_2}\exp(\mu t).
\end{aligned}
$$

Integrating over $[t_0 + \overline{T}_2, t)$ and simplifying gives

$$
\pi_z(t) \leq \exp[-\mu(t - t_0 - \overline{T}_2)] + \left(\frac{1}{2} + \Delta\right)\epsilon\pi^*_z.
$$

Hence provided that t is large enough Lemma 3.9 is true. □

Using these lemmas along with equations (3.7)-(3.9) we find that if Δ is small and positive there exists $\overline{T}_4 > 0$ such that for $t_1 \geq t \geq t_0 + \overline{T}_4$, $0 < \beta_{h_1} < (\frac{1}{2} + \Delta)\epsilon\beta^*_{h_1}$. Similarly there exists $\overline{T}_5 > 0$ such that for $t_1 \geq t \geq t_0 + \overline{T}_2 + \overline{T}_5$, $0 < \beta_{h_2} < (\frac{1}{2} + 2\Delta)\epsilon\beta^*_{h_2}$, and a $\overline{T}_6 > 0$ such that for $t_1 \geq t \geq t_0 + \overline{T}_1 + \overline{T}_6$,

$0 < \beta_y < (\frac{1}{2} + 2\Delta)\epsilon\beta_y^*$. $\overline{T}_4$, $\overline{T}_5$ and $\overline{T}_6$ depend only on the model parameters, Δ and ϵ. We have shown that as π_{h_1} becomes small then all other components become small. We now show that π_{h_1} cannot become arbitrarily small by showing that $t_1 - t_0$ can be bounded above by a fixed finite value and hence π_{h_1} cannot be below $\frac{1}{2}\epsilon\pi_{h_1}^*$ long enough to become arbitrarily close to zero. We have two possibilities: either π_{h_1} stays below $\frac{1}{2}\epsilon\pi_{h_1}^*$ long enough for all the other components to become small or it increases past $\frac{1}{2}\epsilon\pi_{h_1}^*$ before all the other components have become small. We have either

$$(i)\ t_1 \geq t_0 + \max[\overline{T}_1 + \overline{T}_2 + \overline{T}_3, \overline{T}_4, \overline{T}_2 + \overline{T}_5, \overline{T}_1 + \overline{T}_6];\ \text{or}$$
$$(ii)\ t_1 < t_0 + \max[\overline{T}_1 + \overline{T}_2 + \overline{T}_3, \overline{T}_4, \overline{T}_2 + \overline{T}_5, \overline{T}_1 + \overline{T}_6].$$

We want to show that $t_1 - t_0 < T$ where T is a finite value dependent only on the model parameters, Δ and ϵ. If (ii) is true then π_{h_1} increases past $\frac{1}{2}\epsilon\pi_{h_1}^*$ before all the other components have become small and our proof is complete. We now deal with case (i) where t_1 occurs at a time bigger than or equal to the time it takes for all terms to become small. Using the instability of the DFE when $R_0 > 1$ we will show that π_{h_1} cannot stay small indefinitely.

Lemma 3.10. *If $\pi_{h_1}(t)$ drops below $\frac{1}{2}\epsilon\pi_{h_1}^*$ at a time t_0 then $\pi_{h_1}(t)$ returns to this level by at least $t = t_0 + max[\overline{T}_1 + \overline{T}_2 + \overline{T}_3, \overline{T}_4, \overline{T}_2 + \overline{T}_5, \overline{T}_1 + \overline{T}_6, \overline{T}_1 + \overline{T}_2 + \overline{T}_3 + \overline{T}_7]$, which is finite and depends only on the model parameters, Δ and ϵ.*

Proof. Suppose that ϵ_2 is real and positive with $0 < \epsilon_2 < 1$ and consider the matrix $\mathbf{J}(\epsilon_2)$ given by

$$\begin{bmatrix}
-\mu & 0 & 0 & 0 & 0 & 0 & -\lambda(1-\phi)\alpha_h & -\lambda(1-\phi)\alpha_h & -\lambda(1-\phi)\alpha_y \\
0 & -\mu & 0 & \sigma(1-\alpha) & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -(\mu+\sigma) & 0 & 0 & 0 & \lambda(1-\phi)(1-\delta)\alpha_h(1-\epsilon_2) & \lambda(1-\phi)(1-\delta)\alpha_h(1-\epsilon_2) & \lambda(1-\phi)(1-\delta)\alpha_y(1-\epsilon_2) \\
0 & 0 & 0 & -(\mu+\sigma) & 0 & 0 & \lambda(1-\phi)\delta\alpha_h(1-\epsilon_2) & \lambda(1-\phi)\delta\alpha_h(1-\epsilon_2) & \lambda(1-\phi)\delta\alpha_y(1-\epsilon_2) \\
0 & 0 & \sigma & 0 & -\mu & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \sigma\alpha & 0 & -\mu & 0 & 0 & 0 \\
0 & 0 & \lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau) & 0 & 0 \\
0 & 0 & 0 & \lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau) & 0 \\
0 & 0 & 0 & 0 & \lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau)
\end{bmatrix}.$$

When $\epsilon_2 = 0$ we have $\mathbf{J}(0) = \mathbf{J}$ which is the linearised stability matrix that we used to prove the instability of the DFE when $R_0 > 1$. Three of the eigenvalues of this matrix are clearly $-\mu$. Hence we can re-order the rows and columns

so that these eigenvalues are the first three rows and columns of $\mathbf{J}(\epsilon_2)$. Clearly this will not change the eigenvalues of $\mathbf{J}(\epsilon_2)$. For the purpose of calculating the eigenvalues of $\mathbf{J}(\epsilon_2)$, this allows us to rewrite the matrix as follows

$$\mathbf{J}(\epsilon_2) = \begin{bmatrix} -\mu\mathbf{I} & \mathbf{X} \\ \mathbf{0} & \mathbf{J}_1(\epsilon_2) \end{bmatrix}$$

where $\mathbf{I}$ is the 3x3 identity matrix, $\mathbf{0}$ is the 6x3 zero matrix, $\mathbf{X}$ is a 3x6 matrix and $\mathbf{J}_1(\epsilon_2)$=

$$\begin{bmatrix} -(\mu+\sigma) & 0 & 0 & \lambda(1-\phi)(1-\delta)\alpha_h(1-\epsilon_2) & \lambda(1-\phi)(1-\delta)\alpha_h(1-\epsilon_2) & \lambda(1-\phi)(1-\delta)\alpha_y(1-\epsilon_2) \\ 0 & -(\mu+\sigma) & 0 & \lambda(1-\phi)\delta\alpha_h(1-\epsilon_2) & \lambda(1-\phi)\delta\alpha_h(1-\epsilon_2) & \lambda(1-\phi)\delta\alpha_y(1-\epsilon_2) \\ \sigma & 0 & -\mu & 0 & 0 & 0 \\ \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) & 0 & 0 \\ 0 & \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) & 0 \\ 0 & 0 & \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) \end{bmatrix}.$$

Denote the eigenvalues of $\mathbf{J}(\epsilon_2)$ by $\omega_i(\epsilon_2)$, $i = 1, 2, ..., 9$. Now three eigenvalues say $\omega_7 = \omega_8 = \omega_9 = -\mu$ with the other eigenvalues $\omega_i(\epsilon_2)$, $i = 1, 2, ..., 6$ coming from $\mathbf{J}_1(\epsilon_2)$. If we take M large and positive then $\mathbf{J}_1(\epsilon_2)+M\mathbf{I}$ is a non-negative irreducible matrix, with eigenvalues $\omega_i(\epsilon_2)+M, i = 1, 2, .., 6$. Lemma 2.1 from Nold (1980) says that the characteristic equation of this matrix has a simple root that is equal to its spectral radius. If $M+\omega_1(\epsilon_2)$ is the spectral radius eigenvalue of $\mathbf{J}_1(\epsilon_2)+M\mathbf{I}$ then all the other eigenvalues must have smaller real part and $M + \omega_1(\epsilon_2)$ is real. Hence $\omega_1(\epsilon_2)$ is real and all the other eigenvalues of $\mathbf{J}_1(\epsilon_2)$ must have smaller real parts. This is also true when $\epsilon_2 = 0$. Using Corollary 6.6 in Chow and Hale (1982), $\omega_1(\epsilon_2) \to \omega_1(0)$ as $\epsilon_2 \to 0$. In Theorem 3.3 we have shown that $\omega_1(0) > 0$ if $R_0 > 1$ so we can therefore choose ϵ_2 small enough to ensure that $\omega_1(\epsilon_2) > 0$. We can assume, without loss of generality, that $0 < \epsilon_2 < 1$. We can choose ϵ small enough so that

$$\frac{1}{2}\epsilon\pi^*_{h_1} + \left(\frac{1}{2} + \Delta\right)\epsilon\pi^*_{h_2} + \left(\frac{1}{2} + \Delta\right)\epsilon\pi^*_y + \left(\frac{1}{2} + 2\Delta\right)\epsilon\pi^*_z < \epsilon_2. \tag{3.22}$$

Hence for $t_1 > t > t_0 + \overline{T}_1 + \overline{T}_2 + \overline{T}_3$ we have $\pi^+(t) = \pi_{h_1} + \pi_{h_2} + \pi_y + \pi_z < \epsilon_2$. Let $t_2 = \inf\{\zeta \geq 0 : \text{for } t_1 > t > t_0 + \zeta, \quad \pi(t) < \epsilon_2\}$. So if $t_2 > 0$ then by continuity $\pi(t_0 + t_2) = \epsilon_2$ and so $t_0 + t_2$ is the last time before t_1 that $\pi(t) \geq \epsilon_2$.

Note that $t_2 \leq \overline{T}_1 + \overline{T}_2 + \overline{T}_3$. If $t_1 < t_0 + \overline{T}_1 + \overline{T}_2 + \overline{T}_3$ we have the desired result. Consider the case where $t_1 \geq t \geq t_0 + \overline{T}_1 + \overline{T}_2 + \overline{T}_3$. We have that $\frac{d\boldsymbol{x}}{dt} \geq \mathbf{J}_1(\epsilon_2)\boldsymbol{x}$, where $\boldsymbol{x} = (\pi_{h_1}, \pi_{h_2}, \pi_y, \beta_{h_1}, \beta_{h_2}, \beta_y)$. Again using Lemma 2.1 from Nold (1980) we have that for M sufficiently large and positive $M\mathbf{I} + \mathbf{J}_1(\epsilon_2)$ has a strictly positive left eigenvector, $\boldsymbol{e} = (e_1, e_2, e_3, e_4, e_5, e_6)$ which corresponds to the spectral radius $M + \omega_1(\epsilon_2)$. Hence $\boldsymbol{e}$ is also a left eigenvector of $\mathbf{J}_1(\epsilon_2)$ and

$$\boldsymbol{e} \cdot \frac{d\boldsymbol{x}}{dt} \geq \boldsymbol{e} \cdot \mathbf{J}_1(\epsilon_2)\boldsymbol{x} = \omega_1(\epsilon_2)\boldsymbol{e} \cdot \boldsymbol{x}.$$

Thus

$$\begin{aligned}
\boldsymbol{e} \cdot \boldsymbol{x}(t) &\geq (\boldsymbol{e} \cdot \boldsymbol{x})(t_0 + t_2)\exp[\omega_1(\epsilon_2)(t - t_0 - t_2)], \quad \text{(integrating over } [t_0 + t_2, t]), \\
&\geq \pi(t_0 + t_2)\min(e_1, e_2, e_3)\exp[\omega_1(\epsilon_2)(t - t_0 - t_2)], \\
&= \epsilon_2 \min(e_1, e_2, e_3)\exp[\omega_1(\epsilon_2)(t - t_0 - t_2)], \qquad \text{if } t_2 > 0, \\
&\geq \frac{1}{2}\epsilon\pi^*_{h_1}\min(e_1, e_2, e_3)\exp[\omega_1(\epsilon_2)(t - t_0)], \qquad \text{if } t_2 = 0, \text{ and}
\end{aligned}$$

$\pi_{h_1}(\Delta t) \geq \frac{1}{2}\epsilon\pi^*_{h_1}$ so that $\pi_{h_1}(t_0) = \frac{1}{2}\epsilon\pi^*_{h_1}$.

Therefore if $t_2 > 0$ or $\pi_{h_1}(\Delta t) \geq \frac{1}{2}\epsilon\pi^*_{h_1}$ after a time $t_0 + t_2 + \overline{T}_7$ we have

$$\begin{aligned}
\boldsymbol{e} \cdot \boldsymbol{x}(t) > \boldsymbol{e} \cdot \Bigg(& \frac{1}{2}\epsilon\pi^*_{h_1}, \left(\frac{1}{2} + \Delta\right)\epsilon\pi^*_{h_2}, \left(\frac{1}{2} + \Delta\right)\epsilon\pi^*_y, \\
& \left(\frac{1}{2} + \Delta\right)\epsilon\beta^*_{h_1}, \left(\frac{1}{2} + 2\Delta\right)\epsilon\beta^*_{h_2}, \left(\frac{1}{2} + 2\Delta\right)\epsilon\beta^*_y\Bigg),
\end{aligned} \tag{3.23}$$

where $\overline{T}_7$ depends only on ϵ, ϵ_2, Δ and the model parameters. If $t_1 \geq t \geq t_0 + \max[\overline{T}_1 + \overline{T}_2 + \overline{T}_3, \overline{T}_4, \overline{T}_2 + \overline{T}_5, \overline{T}_1 + \overline{T}_6, t_2 + \overline{T}_7]$, the following is true: $\pi_{h_1} \leq \frac{1}{2}\epsilon\pi^*_{h_1}$,$\pi_{h_2} < (\frac{1}{2} + \Delta)\epsilon\pi^*_{h_2}$, $\pi_y < (\frac{1}{2} + \Delta)\epsilon\pi^*_y$, $\pi_z < (\frac{1}{2} + 2\Delta)\epsilon\pi^*_z$, $\beta_{h_1} < (\frac{1}{2} + \Delta)\epsilon\beta^*_{h_1}$, $\beta_{h_2} < (\frac{1}{2} + 2\Delta)\epsilon\beta^*_{h_2}$ and $\beta_y < (\frac{1}{2} + 2\Delta)\epsilon\beta^*_y$. This implies that

$$\begin{aligned}
\boldsymbol{e} \cdot \boldsymbol{x}(t) \leq \boldsymbol{e} \cdot \Bigg(& \frac{1}{2}\epsilon\pi^*_{h_1}, \left(\frac{1}{2} + \Delta\right)\epsilon\pi^*_{h_2}, \left(\frac{1}{2} + \Delta\right)\epsilon\pi^*_y, \\
& \left(\frac{1}{2} + \Delta\right)\epsilon\beta^*_{h_1}, \left(\frac{1}{2} + 2\Delta\right)\epsilon\beta^*_{h_2}, \left(\frac{1}{2} + 2\Delta\right)\epsilon\beta^*_y\Bigg).
\end{aligned}$$

Hence we have a contradiction to (3.23) and so $t_1 < t_0 + \max[\overline{T}_1 + \overline{T}_2 +$

$\overline{T}_3, \overline{T}_4, \overline{T}_2 + \overline{T}_5, \overline{T}_1 + \overline{T}_6, \overline{T}_1 + \overline{T}_2 + \overline{T}_3 + \overline{T}_7]$. We have shown that the first time that π_{h_1} drops below $\frac{1}{2}\epsilon\pi^*_{h_1}$ it must return to this level after a duration of at most $T = \max[\overline{T}_1 + \overline{T}_2 + \overline{T}_3, \overline{T}_4, \overline{T}_2 + \overline{T}_5, \overline{T}_1 + \overline{T}_6, \overline{T}_1 + \overline{T}_2 + \overline{T}_3 + \overline{T}_7]$. We can extend this argument to cover any time when π_{h_1} drops below $\frac{1}{2}\epsilon\pi^*_{h_1}$. Hence if π_{h_1} drops below this level at time $\tilde{t_0}$, then for $t \in [\tilde{t_0}, \tilde{t_0}+T]$

$$\frac{d\pi_{h_1}}{dt} \geq -\pi_{h_1}(\mu + \sigma).$$

Integrating over $[\tilde{t_0}, t)$ we find that in $[\tilde{t_0}, \tilde{t_0}+T]$

$$\pi_{h_1}(t) \geq \frac{1}{2}\epsilon\pi^*_{h_1}\exp[-(\mu + \sigma)T],$$

where T is a fixed duration depending only on ϵ, ϵ_2, Δ and the model parameters. So $\pi_{h_1,\infty} > 0$. By reducing ϵ if necessary we can make $\pi_{h_1,\infty} > \frac{1}{2}\epsilon\pi^*_h$, so the argument at the start of the proof of Theorem 3.4 shows that the result of Theorem 3.4 is true in this case. In the case where $\pi_{h_1}(\Delta t) < \frac{1}{2}\epsilon\pi^*_{h_1}$ the same argument shows that

$$\boldsymbol{e} \cdot \boldsymbol{x}(t) \geq \pi_{h_1}(\Delta t)\min(e_1, e_2, e_3)\exp[\omega_1(\epsilon_2)(t - \Delta t)]$$

so π_{h_1} must eventually rise above $\frac{1}{2}\epsilon\pi^*_{h_1}$ and the above argument holds for subsequent times. □

To prove local stability for the model governing equations would require examining the Routh-Hurwitz conditions for a ninth order polynomial which would be incredibly complicated and difficult to do. Instead we are going to examine the local stability of a closely related approximation model that has only five dimensions. The first idea behind simplifying our system is that an IDU injects on a timescale that is in the order of days where the epidemiological and demographic processes are much slower and measured in years. Examining the needle equations (3.7)-(3.9) we can see that if the prevalence of HCV is constant among each group of the IDU population then HCV prevalence in each group of needles will tend to $\pi_i/(1 + \hat{\tau})$ for $i = h_1, h_2, y$. It is not true that π_{h_1}, π_{h_2} and π_y are fixed but it is true that the β_{h_1}, β_{h_2} and β_y needle equations will respond rapidly to the slowly varying values of π_{h_1}, π_{h_2} and π_y. This allows us to approximate

the dynamic relationship between the IDU and needle classes as $\beta_i \approx \pi_i/(1+\hat{\tau})$ for $i = h_1, h_2, y$. A similar technique was used by Kaplan and O'Keefe (1993) to calculate the reduction in HIV incidence due to the introduction of needle exchange in the "let the needles do the talking model", and by Kaplan (1994, 1995) to justify the assumption that the HIV prevalence amongst IDUs is constant in a model examining the dynamics of HIV in needles. Using this approximation we find that our IDU only model can be represented by the following system of equations:

$$\frac{d\pi_x}{dt} = \mu - \mu\pi_x - \frac{\lambda\pi_x(1-\phi)}{1+\hat{\tau}}(\alpha_h(\pi_{h_1}+\pi_{h_2})+\alpha_y\pi_y), \tag{3.24}$$

$$\frac{d\pi_{x_1}}{dt} = \sigma(1-\alpha)\pi_{h_2} - \mu\pi_{x_1} - \frac{\lambda\pi_{x_1}(1-\phi)}{1+\hat{\tau}}(\alpha_h(\pi_{h_1}+\pi_{h_2})+\alpha_y\pi_y), \tag{3.25}$$

$$\begin{aligned}\frac{d\pi_{h_1}}{dt} &= \frac{\lambda(1-\phi)(1-\delta)}{1+\hat{\tau}}(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h(\pi_{h_1}+\pi_{h_2})+\alpha_y\pi_y)\\ &\quad -(\mu+\sigma)\pi_{h_1},\end{aligned} \tag{3.26}$$

$$\begin{aligned}\frac{d\pi_{h_2}}{dt} &= \frac{\lambda(1-\phi)\delta}{1+\hat{\tau}}(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h(\pi_{h_1}+\pi_{h_2})+\alpha_y\pi_y)\\ &\quad -(\mu+\sigma)\pi_{h_2},\end{aligned} \tag{3.27}$$

$$\frac{d\pi_y}{dt} = \sigma\pi_{h_1} - \mu\pi_y, \tag{3.28}$$

$$\frac{d\pi_z}{dt} = \sigma\alpha\pi_{h_2} - \mu\pi_z. \tag{3.29}$$

The important feature of equations (3.24)-(3.29) is that by construction they have the same equilibrium solutions and R_0 as the full model does. To examine the local stability of this closely related model would require examining the roots of a sixth order polynomial which is still a difficult and complicated task. It is possible to simplify the system further by eliminating the π_x equation. It is known that $1 = \pi_x + \pi_{x_1} + \pi_{h_1} + \pi_{h_2} + \pi_y + \pi_z$ and hence if $\pi_{x_1} \to \pi^*_{x_1}$, $\pi_{h_1} \to \pi^*_{h_1}$, $\pi_{h_2} \to \pi^*_{h_2}$, $\pi_y \to \pi^*_y$ and $\pi_z \to \pi^*_z$ then $\pi_x \to \pi^*_x$. So if everything else is known it is possible to determine the limiting behaviour of π_x. So our closely related model can therefore be represented by equations (3.25)-(3.29).

Theorem 3.5. *The endemic equilibrium of this approximate model is locally stable when $R_0 > 1$.*

Proof. To prove local stability we examine the Jacobian of this system linearised

about the endemic equilibrium. In this resulting stability matrix there is no π_{x_1} term in the other equations. As a result we are able to expand by column one giving the negative eigenvalue $\omega_1 = -\mu - \frac{\lambda(1-\phi)}{1+\hat{\tau}}(\alpha_h(\pi^*_{h_1} + \pi^*_{h_2}) + \alpha_y \pi^*_y)$. Now we are left to find the eigenvalues of the following 4x4 matrix

$$\begin{vmatrix} (1-\delta)ka_1 - (\mu+\sigma+\omega) & (1-\delta)ka_1 & (1-\delta)ka_2 & -(1-\delta)ka_3 \\ \delta k a_1 & \delta k a_1 - (\mu+\sigma+\omega) & \delta k a_2 & -\delta k a_3 \\ \sigma & 0 & -(\mu+\omega) & 0 \\ 0 & \sigma\alpha & 0 & -(\mu+\omega) \end{vmatrix} = 0,$$

where

$$k = \frac{\lambda(1-\phi)}{1+\hat{\tau}},$$

$$a_1 = \alpha_h(1 - 2\pi^*_{h_1} - 2\pi^*_{h_2} - \pi^*_y - \pi^*_z) - \alpha_y \pi^*_y, \tag{3.30}$$

$$a_2 = \alpha_y(1 - \pi^*_{h_1} - \pi^*_{h_2} - 2\pi^*_y - \pi^*_z) - \alpha_h(\pi^*_{h_1} + \pi^*_{h_2}), \tag{3.31}$$

$$a_3 = \alpha_h(\pi^*_{h_1} + \pi^*_{h_2}) + \alpha_y \pi^*_y. \tag{3.32}$$

Since the determinant is unaffected by the use of row and column operations we can make use of these to obtain another negative eigenvalue $\omega_2 = -(\mu + \sigma)$. The remaining eigenvalues satisfy the characteristic equation $\omega^3 + A_1\omega^2 + A_2\omega + A_3 = 0$, where

$$A_1 = 3\mu - ka_1 + \sigma, \tag{3.33}$$

$$A_2 = \sigma\alpha\delta k a_3 + 3\mu^2 - 2\mu k a_1 + 2\mu\sigma - \sigma(1-\delta)ka_2, \tag{3.34}$$

$$A_3 = \mu\sigma\alpha\delta k a_3 + \mu^3 - \mu^2 k a_1 + \mu^2\sigma - \mu\sigma(1-\delta)ka_2. \tag{3.35}$$

Using (3.32) and the equilibrium values (Theorem 3.1) we find that

$$a_3 = K\left(\alpha_h + \frac{\alpha_y \sigma(1-\delta)}{\mu}\right),$$

where K is given by equation (3.12). Performing a similar re-arrangement for (3.30) and (3.31) gives

$$a_1 = \alpha_h\left(1 - \left(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)K\right) - a_3,$$

$$a_2 = \alpha_y \left(1 - \left(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right) K\right) - a_3.$$

Substituting in for K and re-arranging gives

$$A_1 = 2\mu + \frac{\alpha_y(\mu+\sigma)\sigma(1-\delta)}{\mu\left(\alpha_h + \frac{\alpha_y\sigma(1-\delta)}{\mu}\right)} + ka_3, \tag{3.36}$$

$$A_2 = \mu^2 + \frac{\sigma(1-\delta)\alpha_y(\mu+\sigma)}{\left(\alpha_h + \frac{\alpha_y\sigma(1-\delta)}{\mu}\right)} + ka_3[2\mu + \delta\alpha\sigma + \sigma(1-\delta)], \tag{3.37}$$

$$A_3 = \mu k a_3[\mu + \delta\sigma\alpha + \sigma(1-\delta)]. \tag{3.38}$$

Using the Routh-Hurwitz conditions for a cubic polynomial we are required to show that $A_1 > 0$, $A_3 > 0$ and $A_1A_2 > A_3$. Since all parameters represent positive rates of flow and $a_3 > 0$, $\delta \leq 1$ we can say that $A_1 > 2\mu > 0$ as required. Using the same argument we can also conclude that $A_3 > 0$. We can also go one further and apply the argument to the expression for A_2 given by (3.37), which confirms that $A_2 > 0$.

The final stage of the Routh-Hurwitz conditions for a cubic polynomial require $A_1A_2 > A_3$. If we examine the expressions for A_1 and A_2 given by (3.36) and (3.37) respectively and multiply them together we obtain,

$$\left[2\mu + \frac{(\mu+\sigma)\sigma(1-\delta)\alpha_y}{\left(\alpha_h + \frac{\alpha_y\sigma(1-\delta)}{\mu}\right)\mu} + ka_3\right]\left[\mu^2 + \frac{\sigma(1-\delta)\alpha_y(\mu+\sigma)}{\left(\alpha_h + \frac{\alpha_y\sigma(1-\delta)}{\mu}\right)} + ka_3[2\mu + \delta\sigma\alpha + \sigma(1-\delta)]\right],$$

$$\begin{aligned} &> \mu^2 k a_3 + 2\mu k a_3[2\mu + \delta\sigma\alpha + \sigma(1-\delta)], \\ &= 5\mu^2 k a_3 + 2\mu\delta\sigma\alpha k a_3 + 2\mu\sigma(1-\delta)ka_3, \\ &> A_3. \end{aligned}$$

Hence if $R_0 > 1$ then $A_1 > 0$, $A_3 > 0$ and $A_1A_2 > A_3$ and therefore the Routh-Hurwitz conditions are satisfied and the endemic equilibrium in this IDU only model is locally stable. □

It is possible to make this approximation more rigorous by showing that if $\lambda\gamma$ gets large compared with the other model parameters apart from τ, then three of

the roots of the characteristic equation of the Jacobian of the full model at the endemic equilibrium are close to $-(\lambda\gamma+\tau)$ and the other six roots are close to the roots of the characteristic of the Jacobian of the IDU only model evaluated at the endemic equilibrium. Arguing as in the IDU only model it is possible to eliminate the π_x equation from the full model because of its linear dependency. Furthermore, since there is no π_{x_1} term in the other equations we can obtain the negative eigenvalue $\omega_1 = -\mu - \frac{\lambda(1-\phi)}{1+\hat{\tau}}(\alpha_h(\pi^*_{h_1}+\pi^*_{h_2})+\alpha_y\pi^*_y)$ as in the IDU only model. Row and column operations can then be used to give another eigenvalue $\omega_2 = -(\mu+\sigma)$ again as in the IDU only model, leaving us to examine

$$\det \mathbf{J}_2(\omega) = 0$$

where the 6x6 matrix $\mathbf{J}_2(\omega)$ is given by

$$\begin{bmatrix}
-(\mu+\sigma+\omega)+B_1 & \delta B_1 & \delta B_1 & \delta\alpha_h B_2 & \delta\alpha_h B_2 & \delta\alpha_y B_2 \\
\frac{\sigma(1-\delta)}{\delta} & -\mu-\omega & 0 & 0 & 0 & 0 \\
\sigma\alpha & 0 & -\mu-\omega & 0 & 0 & 0 \\
\frac{\lambda\gamma(1-\delta)}{\delta} & 0 & 0 & -(\lambda+\gamma+\tau+\omega) & 0 & 0 \\
\lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau+\omega) & 0 \\
0 & \lambda\gamma & 0 & 0 & 0 & -(\lambda\gamma+\tau+\omega)
\end{bmatrix}$$

where $B_1 = -\lambda(1-\phi)(\alpha_h(\beta_{h_1^*}+\beta^*_{h_2})+\alpha_y\beta^*_y)$ and $B_2 = \lambda(1-\phi)(1-\pi^*_{h_1}-\pi^*_{h_2}-\pi^*_y-\pi^*_z)$. We again use the fact that the determinant is unaffected by row and column operations to obtain $\det \mathbf{J}_2(\omega)$=$\det \mathbf{J}_3(\omega)$ where the matrix $\mathbf{J}_3(\omega)$ is the matrix $\mathbf{J}_2(\omega)$ with

$$C_1' = C_1 + \frac{(1-\delta)}{\delta}\frac{C_4}{1+\hat{\tau}} + \frac{C_5}{1+\hat{\tau}}, \text{ and}$$
$$C_2' = C_2 + \frac{C_6}{1+\hat{\tau}}.$$

Columns 3,4,5 and 6 in $\mathbf{J}_3(\omega)$ are the same as in matrix $\mathbf{J}_2(\omega)$. Hence the matrix $\mathbf{J}_3(\omega)$ is given by

$$\begin{bmatrix} -(\mu+\sigma+\omega)+B_1+\frac{B_2\alpha_h}{1+\hat{\tau}} & \delta B_1+\frac{B_2\delta\alpha_y}{1+\hat{\tau}} & \delta B_1 & \delta\alpha_h B_2 & \delta\alpha_h B_2 & \delta\alpha_y B_2 \\ \frac{\sigma(1-\delta)}{\delta} & -\mu-\omega & 0 & 0 & 0 & 0 \\ \sigma\alpha & 0 & -\mu-\omega & 0 & 0 & 0 \\ \frac{-\omega(1-\delta)}{\delta(1+\hat{\tau})} & 0 & 0 & -(\lambda\gamma+\tau+\omega) & 0 & 0 \\ \frac{-\omega}{1+\hat{\tau}} & 0 & 0 & 0 & -(\lambda\gamma+\tau+\omega) & 0 \\ 0 & \frac{-\omega}{1+\hat{\tau}} & 0 & 0 & 0 & -(\lambda\gamma+\tau+\omega) \end{bmatrix}.$$

We have that $\det \mathbf{J}_3 = (\lambda\gamma+\tau+\omega)^3 \det \mathbf{A}$ plus terms involving at most $(\lambda\gamma+\tau+\omega)^2$, where $\det \mathbf{A} = 0$ is the characteristic equation of our IDU only model about the endemic equilibrium. If $\lambda\gamma \to \infty$ with $\hat{\tau} = \tau/\lambda\gamma$ fixed then

$$\frac{\det \mathbf{J}_3}{(\lambda\gamma+\tau+\omega)^3 \det \mathbf{A}} \to 1.$$

Therefore the roots of the characteristic equation of the full transmission model about the endemic equilibrium tend to the roots of the characteristic equation of the IDU only model. The other three each tend to $-(\lambda\gamma+\tau)$. Hence if $\lambda\gamma$ gets large then all eigenvalues have strictly negative real parts and the endemic equilibrium of the full HCV transmission model is locally stable when $R_0 > 1$.

3.5 Global stability

Due to the complexity of our transmission model we have been unable to show that, provided that $R_0 > 1$ and HCV is present in the population, our model tends to its endemic equilibrium without imposing extra conditions. However we shall see later that simulations suggest that this is indeed the case and we are now going to derive sufficient conditions for global stability of the endemic equilibrium of our HCV transmission model. It is worth noting that this equilibrium, which is possible if and only if $R_0 > 1$, cannot be absolutely globally stable, since the system cannot take off if there is no HCV initially present in the population.

To derive the conditions for global stability we follow an argument similar to that used in Greenhalgh and Lewis (2000) and consider a translated co-ordinate system $(\tilde{\pi}_x, \tilde{\pi}_{x_1}, \tilde{\pi}_{h_1}, \tilde{\pi}_{h_2}, \tilde{\pi}_y, \tilde{\pi}_z, \tilde{\beta}_{h_1}, \tilde{\beta}_{h_2}, \tilde{\beta}_y)$, where $\tilde{\pi}_i = \pi_i - \pi_i^*$ for $i = x, x_1, h_1, h_2, y, z$ and $\tilde{\beta}_j = \beta_j - \beta_j^*$ for $j = h_1, h_2, y$. The origin of this new co-ordinate system is the endemic equilibrium $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*, \beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*)$.

We begin with the following equations:

$$\frac{d\pi_h}{dt} = \lambda(1-\phi)(1-\pi_h-\pi_y-\pi_z)(\alpha_h\beta_h+\alpha_y\beta_y) - (\mu+\sigma)\pi_h, \tag{3.39}$$

$$\frac{d\pi_y}{dt} = \sigma(1-\delta)\pi_h - \mu\pi_y, \tag{3.40}$$

$$\frac{d\pi_z}{dt} = \sigma\alpha\delta\pi_h - \mu\pi_z, \tag{3.41}$$

$$\frac{d\beta_h}{dt} = \lambda\gamma(\pi_h-\beta_h) - \tau\beta_h, \tag{3.42}$$

$$\frac{d\beta_y}{dt} = \lambda\gamma(\pi_y-\beta_y) - \tau\beta_y, \tag{3.43}$$

where $\pi_h = \pi_{h_1} + \pi_{h_2}$ and $\beta_h = \beta_{h_1} + \beta_{h_2}$. Applying the suggested translation to equations (3.39)-(3.43) gives the following system of equations:

$$\begin{aligned}\frac{d\tilde{\pi}_h}{dt} &= \lambda(1-\phi)(1-\pi_h^*-\pi_y^*-\pi_z^*)(\alpha_h\tilde{\beta}_h+\alpha_y\tilde{\beta}_y)\\ &\quad - \lambda(1-\phi)(\tilde{\pi}_h+\tilde{\pi}_y+\tilde{\pi}_z)(\alpha_h\beta_h+\alpha_y\beta_y) - (\mu+\sigma)\tilde{\pi}_h,\end{aligned} \tag{3.44}$$

$$\frac{d\tilde{\pi}_y}{dt} = \sigma(1-\delta)\tilde{\pi}_h - \mu\tilde{\pi}_y, \tag{3.45}$$

$$\frac{d\tilde{\pi}_z}{dt} = \sigma\alpha\delta\tilde{\pi}_h - \mu\tilde{\pi}_z, \tag{3.46}$$

$$\frac{d\tilde{\beta}_h}{dt} = \lambda\gamma(\tilde{\pi}_h-\tilde{\beta}_h) - \tau\tilde{\beta}_h, \tag{3.47}$$

$$\frac{d\tilde{\beta}_y}{dt} = \lambda\gamma(\tilde{\pi}_y-\tilde{\beta}_y) - \tau\tilde{\beta}_y. \tag{3.48}$$

Our aim is to show that $(\tilde{\pi}_h, \tilde{\pi}_y, \tilde{\pi}_z, \tilde{\beta}_h, \tilde{\beta}_y) \to (0,0,0,0,0)$ as $t \to \infty$. This is equivalent to $(\pi_h, \pi_y, \pi_z, \beta_h, \beta_y) \to (\pi_h^*, \pi_y^*, \pi_z^*, \beta_h^*, \beta_y^*)$ as $t \to \infty$. We can write the system of equations (3.44)-(3.48) in the form

$$\frac{d\tilde{\boldsymbol{x}}}{dt} = \mathbf{V}(\boldsymbol{x})\tilde{\boldsymbol{x}},$$

where $\boldsymbol{x}^T = (\pi_h, \pi_y, \pi_z, \beta_h, \beta_y)$, $\tilde{\boldsymbol{x}}^T = (\tilde{\pi}_h, \tilde{\pi}_y, \tilde{\pi}_z, \tilde{\beta}_h, \tilde{\beta}_y)$ and

$$\mathbf{V}(\boldsymbol{x}) = \begin{bmatrix} -B_3 - (\mu+\sigma) & -B_3 & -B_3 & B_4\alpha_h & B_4\alpha_y \\ \sigma(1-\delta) & -\mu & 0 & 0 & 0 \\ \sigma\alpha\delta & 0 & -\mu & 0 & 0 \\ \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) & 0 \\ 0 & \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) \end{bmatrix},$$

where $B_3 = \lambda(1-\phi)(\alpha_h\beta_h + \alpha_y\beta_y)$ and $B_4 = \lambda(1-\phi)(1-\pi_h^* - \pi_y^* - \pi_z^*)$. When $\boldsymbol{x} = \boldsymbol{0}$ we have the following:

$$\mathbf{V}(\boldsymbol{0}) = \begin{bmatrix} -(\mu+\sigma) & 0 & 0 & B_4\alpha_h & B_4\alpha_y \\ \sigma(1-\delta) & -\mu & 0 & 0 & 0 \\ \sigma\alpha\delta & 0 & -\mu & 0 & 0 \\ \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) & 0 \\ 0 & \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) \end{bmatrix},$$

where the only strictly negative entries are on the main diagonal of the matrix. We introduce another co-ordinate system $(\tilde{\pi}, \tilde{\pi}_y, \tilde{\pi}_z, \tilde{\beta}_h, \tilde{\beta}_y)$, where $\tilde{\pi} = \tilde{\pi}_h + \tilde{\pi}_y + \tilde{\pi}_z$. This system is easily obtained from the translated system by adding together equations (3.44), (3.45) and (3.46) and replacing $\tilde{\pi}_h$ by $\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z$. Therefore our second translated system has the following governing equations:

$$\begin{aligned}
\frac{d\tilde{\pi}}{dt} &= \lambda(1-\phi)(1-\pi_h^* - \pi_y^* - \pi_z^*)(\alpha_h\tilde{\beta}_h + \alpha_y\tilde{\beta}_y) - \mu\tilde{\pi} \\
&\quad - \lambda(1-\phi)(\alpha_h\beta_h + \alpha_y\beta_y)\tilde{\pi} - (\sigma\delta - \sigma\alpha\delta)(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z), \\
\frac{d\tilde{\pi}_y}{dt} &= \sigma(1-\delta)(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z) - \mu\tilde{\pi}_y, \\
\frac{d\tilde{\pi}_z}{dt} &= \sigma\alpha\delta(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z) - \mu\tilde{\pi}_z, \\
\frac{d\tilde{\beta}_h}{dt} &= \lambda\gamma(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z - \tilde{\beta}_h) - \tau\tilde{\beta}_h, \\
\frac{d\tilde{\beta}_y}{dt} &= \lambda\gamma(\tilde{\pi}_y - \tilde{\beta}_y) - \tau\tilde{\beta}_y.
\end{aligned}$$

This system of equations can be expressed in the form

$$\frac{d\tilde{\boldsymbol{y}}}{dt} = \mathbf{W}(\boldsymbol{y})\tilde{\boldsymbol{y}},$$

where $\boldsymbol{y}^T = (\pi, \pi_y, \pi_z, \beta_h, \beta_y)$, $\tilde{\boldsymbol{y}}^T = (\tilde{\pi}, \tilde{\pi}_y, \tilde{\pi}_z, \tilde{\beta}_h, \tilde{\beta}_y)$ and $\mathbf{W}(\boldsymbol{y}) =$

$$\begin{bmatrix} -B_3 - \mu - (\sigma\delta - \sigma\delta\alpha) & \sigma\delta - \sigma\delta\alpha & \sigma\delta - \sigma\delta\alpha & B_4\alpha_h & B_4\alpha_y \\ \sigma(1-\delta) & -(\sigma(1-\delta)+\mu) & -\sigma(1-\delta) & 0 & 0 \\ \sigma\alpha\delta & -\sigma\alpha\delta & -(\sigma\alpha\delta+\mu) & 0 & 0 \\ \lambda\gamma & -\lambda\gamma & -\lambda\gamma & -(\lambda\gamma+\tau) & 0 \\ 0 & \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) \end{bmatrix},$$

where the variables $\beta_h(t)$ and $\beta_y(t)$ only appear in the main diagonal. While $\mathbf{V}(\boldsymbol{x})$ has non-negative entries except on the main diagonal when $\boldsymbol{x} = \boldsymbol{0}$, $\mathbf{W}(\boldsymbol{y})$ has constant entries except on the main diagonal. Even though these matrices have different structures they share an important property which we now show.

Lemma 3.11. *$\boldsymbol{V(x)}$ and $\boldsymbol{W(y)}$ have the same eigenvalues.*

Proof.

$$\tilde{\boldsymbol{y}} = \mathbf{J}\tilde{\boldsymbol{x}}, \text{ where } \mathbf{J} = \begin{bmatrix} 1 & 1 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}.$$

It is straightforward to show that $\mathbf{V}(\boldsymbol{x}) = \mathbf{J}^{-1}\mathbf{W}(\boldsymbol{y})\mathbf{J}$. Therefore if $\boldsymbol{e}$ is a right eigenvector of $\mathbf{V}(\boldsymbol{x})$ with corresponding eigenvalue ω, then $\mathbf{J}\boldsymbol{e}$ is a right eigenvector of $\mathbf{W}(\boldsymbol{y})$ with the same corresponding eigenvalue ω. Similarly, if $\boldsymbol{f}$ is a right eigenvector of $\mathbf{W}(\boldsymbol{y})$ with corresponding eigenvalue ω, then $\mathbf{J}^{-1}\boldsymbol{f}$ is the corresponding right eigenvector of $\mathbf{V}(\boldsymbol{x})$ with the same eigenvalue. Hence the two matrices $\mathbf{V}(\boldsymbol{x})$ and $\mathbf{W}(\boldsymbol{y})$ have the same eigenvalues. □

We now consider the system given by $\mathbf{W}(\boldsymbol{y})$. Using Theorem 3.4 we can replace $\beta_h(t)$, $\beta_y(t)$ in $\mathbf{W}(\boldsymbol{y})$ by a fixed small positive ϵ. We define $\mathbf{W}^+ =$

$$\begin{bmatrix} -\hat{B}_3 - \mu - (\sigma\delta - \sigma\delta\alpha) & \sigma\delta - \sigma\delta\alpha & \sigma\delta - \sigma\delta\alpha & B_4\alpha_h & B_4\alpha_y \\ \sigma(1-\delta) & -(\sigma(1-\delta)+\mu) & -\sigma(1-\delta) & 0 & 0 \\ \sigma\alpha\delta & -\sigma\alpha\delta & -(\sigma\alpha\delta+\mu) & 0 & 0 \\ \lambda\gamma & -\lambda\gamma & -\lambda\gamma & -(\lambda\gamma+\tau) & 0 \\ 0 & \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau) \end{bmatrix},$$

where $\hat{B_3} = \lambda(1-\phi)(\alpha_h + \alpha_y)\epsilon$. Therefore for $t \geq \eta$, we have $\mathbf{W}(\boldsymbol{y}) \leq \mathbf{W}^+$. Define

$$\mathbf{E} = \begin{bmatrix} \lambda(1-\phi)(\alpha_h+\alpha_y) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

This allows us to write $\mathbf{W}^+$ as $\mathbf{W}(\boldsymbol{0}) - \epsilon\mathbf{E}$. Note that $\mathbf{W}(\boldsymbol{0})$ and $\mathbf{V}(\boldsymbol{0})$ have the same eigenvalues (Lemma 3.11). We are now going to follow an argument similar to the proof of Theorem 3.4 in order to show that $\mathbf{W}^+$ is Lyapunov stable, that is all solutions starting near an equilibrium point will remain near the equilibrium point (Jordan and Smith 1987).

Using the equilibrium equations to the system (3.39)-(3.43) we see that $\mathbf{V}(\boldsymbol{0})$ has a strictly positive eigenvector $(\pi_h^*, \pi_y^*, \pi_z^*, \beta_h^*, \beta_y^*)$ with corresponding eigenvalue zero. The eigenvalues of $\mathbf{V}(\boldsymbol{0})$ are $\omega = -\mu$ and the eigenvalues of $\overline{\mathbf{V}}(\boldsymbol{0})$ where $\overline{\mathbf{V}}(\boldsymbol{0})$ is given by

$$\begin{bmatrix} -(\mu+\sigma) & 0 & B_4\alpha_h & B_4\alpha_y \\ \sigma(1-\delta) & -\mu & 0 & 0 \\ \lambda\gamma & 0 & -(\lambda\gamma+\tau) & 0 \\ 0 & \lambda\gamma & 0 & -(\lambda\gamma+\tau) \end{bmatrix},$$

which is irreducible and has positive eigenvector $(\pi_h^*, \pi_y^*, \beta_h^*, \beta_y^*)$. If M is sufficiently large then $\overline{\mathbf{V}}(\boldsymbol{0}) + M\mathbf{I}$ (where $\mathbf{I}$ is the 4x4 identity matrix) is an irreducible matrix with non-negative entries and a unique strictly positive eigenvector $(\pi_h^*, \pi_y^*, \beta_h^*, \beta_y^*)$. Lemma 2.1 in Nold (1980) states that the eigenvalue corresponding to this eigenvector of $\overline{\mathbf{V}}(\boldsymbol{0}) + M\mathbf{I}$ is a simple eigenvalue equal to the spectral radius of $\overline{\mathbf{V}}(\boldsymbol{0}) + M\mathbf{I}$. Therefore zero is a simple eigenvalue of $\overline{\mathbf{V}}(\boldsymbol{0})$ and all other eigenvalues have strictly negative real parts. Hence as the eigenvalues of $\mathbf{V}(\boldsymbol{0})$ are the eigenvalues of $\overline{\mathbf{V}}(\boldsymbol{0})$ and $\omega = -\mu$ we see that zero is a simple eigenvalue of $\mathbf{V}(\boldsymbol{0})$ and all other eigenvalues have strictly negative real parts. The same can be said for $\mathbf{W}(\boldsymbol{0})$ since it has the same eigenvalues as $\mathbf{V}(\boldsymbol{0})$.

The characteristic equation of $\mathbf{W}^+ = \mathbf{W}(\boldsymbol{0}) - \epsilon\mathbf{E}$ is given by

$$\omega^5 + a_1(\epsilon)\omega^4 + a_2(\epsilon)\omega^3 + a_3(\epsilon)\omega^2 + a_4(\epsilon)\omega + a_5 = 0, \tag{3.49}$$

where $a_i(\epsilon),\ i = 1, 2, 3, 4$ are continuous functions of ϵ. It is straightforward to show that the constant term a_5 in the characteristic equation is given by

$$\begin{aligned} -B_4\alpha_y\lambda\gamma(\lambda\gamma+\tau)\sigma(1-\delta)\mu - (\lambda\gamma+\tau)B_4\alpha_h\lambda\gamma\mu^2 + (\lambda\gamma+\tau)^2(\mu^2\sigma+\mu^3) \\ +(\lambda\gamma+\tau)^2\hat{B}_3[\mu\sigma(1-\delta)+\mu^2+\sigma\alpha\delta\mu], \end{aligned}$$

where $B_4 = \lambda(1-\phi)(1-\pi_h^*-\pi_y^*-\pi_z^*)$, $\hat{B}_3 = \lambda(1-\phi)(\alpha_h+\alpha_y)\epsilon$. Substituting in for $\hat{B}_3$ gives

$$\begin{aligned} a_5 = -B_4\alpha_y\lambda\gamma(\lambda\gamma+\tau)\sigma(1-\delta)\mu - (\lambda\gamma+\tau)B_4\alpha_h\lambda\gamma\mu^2 + (\lambda\gamma+\tau)^2(\mu^2\sigma+\mu^3) \\ +(\lambda\gamma+\tau)^2\lambda(1-\phi)(\alpha_h+\alpha_y)\epsilon[\mu\sigma(1-\delta)+\mu^2+\sigma\alpha\delta\mu], \end{aligned}$$

which can be written as

$$a_5(\epsilon) = a_5(0) + k_1\epsilon, \tag{3.50}$$

where $k_1 = (\lambda\gamma+\tau)^2\lambda(1-\phi)(\alpha_h+\alpha_y)[\mu\sigma(1-\delta)+\mu^2+\sigma\alpha\delta\mu]$.

Let $\{\omega_1, \omega_2, \omega_3, \omega_4, \omega_5\}$ denote the eigenvalues of the characteristic equation (3.49). When $\epsilon = 0$, $\mathbf{W}^+ = \mathbf{W}(\boldsymbol{0})$. Since zero is an eigenvalue of $\mathbf{W}(\boldsymbol{0})$ one eigenvalue, ω_5 say, must be zero while the other four eigenvalues ($\omega_1, \omega_2, \omega_3$ and ω_4) must have negative real parts.

We now examine the case where we have a small $\epsilon > 0$. Since all eigenvalues are continuous in ϵ, four of our eigenvalues ($\omega_1, \omega_2, \omega_3$ and ω_4) will still have negative real parts. Suppose that the fifth eigenvalue, ω_5 say, has non-negative real part. Hence we have $a_5 = -\omega_1\omega_2\omega_3\omega_4\omega_5 \leq 0$. Turning to (3.50) we see that for small positive ϵ and $k_1 > 0$ $a_5(\epsilon)$ is increasing in ϵ and hence $a_5(\epsilon) > 0$ which implies the last remaining eigenvalue $\omega_5 < 0$. Therefore, for small $\epsilon > 0$, all the eigenvalues of $\mathbf{W}^+$ have negative real parts and hence $\mathbf{W}^+$ is Lyapunov stable.

There is a theorem of Lyapunov which states that all the eigenvalues of a matrix $\mathbf{G}$ will have negative real parts if and only if there exists a symmetric

positive definite matrix $\mathbf{H}$ such that

$$\mathbf{GH} + \mathbf{HG}^T \tag{3.51}$$

is negative definite (Barker *et al.* 1978). Hence there exists a symmetric positive definite matrix $\mathbf{R}$ such that

$$\mathbf{W}^+\mathbf{R} + \mathbf{R}\mathbf{W}^{+^T} = -\mathbf{S} \tag{3.52}$$

where $\mathbf{S}$ is a positive definite matrix. Lyapunov stability tells us that if our system starts near the endemic equilibrium and the solutions converge to this equilibrium then the system is locally asymptotically stable. This result is not enough to show global stability for our endemic equilibrium. We require $\mathbf{W}^+$ to be Volterra-Lyapunov stable, meaning that (3.51) holds for a positive diagonal matrix $\mathbf{H}$. Volterra-Lyapunov stability implies the strongest stability property (Chu 2007) namely that our system has a globally stable equilibrium.

Barker *et al.* (1978) show that, for any matrix $\mathbf{G}$, there exists a positive diagonal matrix $\mathbf{H}$ that satisfies (3.51) if $\mathbf{G}$ has a positive diagonal and $\mathbf{M}(\mathbf{G})$ is given by

$$\mathbf{M}(\mathbf{G})_{ij} = \begin{cases} |\boldsymbol{G}_{ij}| & \text{if} \quad i = j, \\ -|\boldsymbol{G}_{ij}| & \text{if} \quad i \neq j \end{cases}$$

is a non-singular M-matrix. By definition a non-singular M-matrix is a matrix that has off-diagonal entries that are zero or negative and leading principal minors that are positive. Define $\mathbf{T} = -\mathbf{W}^{+^T}$. Then $\mathbf{M}(\mathbf{T})=$

$$\begin{bmatrix} \hat{B}_3 + \mu + (\sigma\delta - \sigma\delta\alpha) & -\sigma(1-\delta) & -\sigma\delta\alpha & -\lambda\gamma & 0 \\ -\sigma\delta + \sigma\delta\alpha & \sigma(1-\delta) + \mu & -\sigma\delta\alpha & -\lambda\gamma & -\lambda\gamma \\ -\sigma\delta + \sigma\alpha\delta & -\sigma(1-\delta) & \sigma\alpha\delta + \mu & -\lambda\gamma & 0 \\ -B_4\alpha_h & 0 & 0 & \lambda\gamma + \tau & 0 \\ -B_4\alpha_y & 0 & 0 & 0 & \lambda\gamma + \tau \end{bmatrix}.$$

Examining $\mathbf{M}(\mathbf{T})$ we see that all off-diagonal entries are zero or negative, as required. We will now find a necessary and sufficient condition for all leading

principal minors to be positive. We find that we require $\det(\mathbf{M}(\mathbf{T}))= (\lambda\gamma + \tau)\det\mathbf{M}_1 - B_4\alpha_y\det\mathbf{M}_2 > 0$, since this would imply that all other leading principal minors are positive. Here

$$\mathbf{M}_1 = \begin{bmatrix} \hat{B_3} + \mu + (\sigma\delta - \sigma\delta\alpha) & -\sigma(1-\delta) & -\sigma\delta\alpha & -\lambda\gamma \\ -\sigma\delta + \sigma\delta\alpha & \sigma(1-\delta) + \mu & -\sigma\delta\alpha & -\lambda\gamma \\ -\sigma\delta + \sigma\alpha\delta & -\sigma(1-\delta) & \sigma\alpha\delta + \mu & -\lambda\gamma \\ -B_4\alpha_h & 0 & 0 & \lambda\gamma + \tau \end{bmatrix},$$

and

$$\mathbf{M}_2 = \begin{bmatrix} -\sigma(1-\delta) & -\sigma\delta\alpha & -\lambda\gamma & 0 \\ \sigma(1-\delta) + \mu & -\sigma\delta\alpha & -\lambda\gamma & -\lambda\gamma \\ -\sigma(1-\delta) & \sigma\alpha\delta + \mu & -\lambda\gamma & 0 \\ 0 & 0 & \lambda\gamma + \tau & 0 \end{bmatrix}.$$

It is straightforward to show that $\det(\mathbf{M}_2) = \lambda\gamma(\lambda\gamma+\tau)\sigma(1-\delta)(2\sigma\alpha\delta+\mu) > 0$. Hence $\det(\mathbf{M}(\mathbf{T}))> 0$ implies that $\det(\mathbf{M}_1) > 0$. We can re-write $\det(\mathbf{M}_1) = (\lambda\gamma + \tau)\det\mathbf{M}_3 + B_4\alpha_h\det\mathbf{M}_4$, where the matrices $\mathbf{M}_3$ and $\mathbf{M}_4$ are as follows:

$$\mathbf{M}_3 = \begin{bmatrix} \hat{B_3} + \mu + (\sigma\delta - \sigma\delta\alpha) & -\sigma(1-\delta) & -\sigma\delta\alpha \\ -\sigma\delta + \sigma\delta\alpha & \sigma(1-\delta) + \mu & -\sigma\delta\alpha \\ -\sigma\delta + \sigma\alpha\delta & -\sigma(1-\delta) & \sigma\alpha\delta + \mu \end{bmatrix},$$

and

$$\mathbf{M}_4 = \begin{bmatrix} -\sigma(1-\delta) & -\sigma\delta\alpha & -\lambda\gamma \\ \sigma(1-\delta) + \mu & -\sigma\delta\alpha & -\lambda\gamma \\ -\sigma(1-\delta) & \sigma\alpha\delta + \mu & -\lambda\gamma \end{bmatrix}.$$

Using row operations we find that $\det(\mathbf{M}_4) = -\lambda\gamma(2\sigma\alpha\delta + \mu)(2\sigma(1-\delta) + \mu) < 0$. Therefore for all leading principal minors to be strictly positive we require $\det(\mathbf{M}(\mathbf{T}))> 0$ which implies that $\det(\mathbf{M}_1) >0$ which in turn implies that $\det(\mathbf{M}_3) > 0$. If this condition is satisfied, all leading principal minors are strictly positive and (3.52) is satisfied with $\mathbf{R}$ a positive diagonal matrix. Hence, provided that $R_0 > 1$ and $\det(\mathbf{M}(\mathbf{T}))> 0$, the system $(\pi_h, \pi_y, \pi_z, \beta_h, \beta_y) \to (\pi_h^*, \pi_y^*, \pi_z^*, \beta_h^*, \beta_y^*)$ as $t \to \infty$.

We now show that the system $(\pi_{h_1}, \pi_{h_2}, \pi_y, \pi_z, \beta_h, \beta_y) \to (\pi^*_{h_1}, \pi^*_{h_2}, \pi^*_y, \pi^*_z, \beta^*_h, \beta^*_y)$ as $t \to \infty$ provided $R_0 > 1$ and a matrix sufficiency condition is satisfied. We begin with the following set of equations:

$$\begin{aligned}\frac{d\pi_{h_1}}{dt} &= \lambda(1-\phi)(1-\delta)(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h\beta_h+\alpha_y\beta_y) \\ &\quad -(\mu+\sigma)\pi_{h_1},\end{aligned} \tag{3.53}$$

$$\begin{aligned}\frac{d\pi_{h_2}}{dt} &= \lambda(1-\phi)\delta(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)(\alpha_h\beta_h+\alpha_y\beta_y) \\ &\quad -(\mu+\sigma)\pi_{h_2},\end{aligned} \tag{3.54}$$

$$\frac{d\pi_y}{dt} = \sigma\pi_{h_1} - \mu\pi_y, \tag{3.55}$$

$$\frac{d\pi_z}{dt} = \sigma\alpha\pi_{h_2} - \mu\pi_z, \tag{3.56}$$

$$\frac{d\beta_h}{dt} = \lambda\gamma(\pi_{h_1}+\pi_{h_2}-\beta_h) - \tau\beta_h, \tag{3.57}$$

$$\frac{d\beta_y}{dt} = \lambda\gamma(\pi_y-\beta_y) - \tau\beta_y. \tag{3.58}$$

From (3.15) we have $\delta\pi_{h_1} - (1-\delta)\pi_{h_2} = f(t)$ where $f(t) \to 0$ as $t \to \infty$. Hence

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

Using these relationships, along with equations (3.53)-(3.58) we obtain

$$\begin{aligned}\frac{d\pi_h}{dt} &= \lambda(1-\phi)(1-\delta)(1-\pi_h-\pi_y-\pi_z)(\alpha_h\beta_h+\alpha_y\beta_y) \\ &\quad -(\mu+\sigma)\pi_h,\end{aligned} \tag{3.59}$$

$$\frac{d\pi_y}{dt} = \sigma(1-\delta)\pi_h + \sigma f(t) - \mu\pi_y, \tag{3.60}$$

$$\frac{d\pi_z}{dt} = \sigma\alpha\delta\pi_h - \sigma\alpha f(t) - \mu\pi_z, \tag{3.61}$$

$$\frac{d\beta_h}{dt} = \lambda\gamma(\pi_h-\beta_h) - \tau\beta_h, \tag{3.62}$$

$$\frac{d\beta_y}{dt} = \lambda\gamma(\pi_y-\beta_y) - \tau\beta_y. \tag{3.63}$$

Using a similar linearisation technique to that used previously we write this sys-

tem in the form

$$\frac{d\tilde{\boldsymbol{x}}}{dt} = \mathbf{V}(\boldsymbol{x})\tilde{\boldsymbol{x}} + \boldsymbol{f}_{\boldsymbol{x}},$$

where $\mathbf{V}(\boldsymbol{x})$ is the same matrix calculated earlier and $\boldsymbol{f}_{\boldsymbol{x}}^T = (0, \sigma f, -\sigma\alpha f, 0, 0)$. Since the matrix $\mathbf{V}(\boldsymbol{x})$ is unchanged the properties shown earlier still hold. We again need to introduce another co-ordinate system in order to complete the proof. This new system is obtained by adding together equations (3.59)-(3.61) to obtain a differential equation for $d\tilde{\pi}/dt$ which replaces the one for $d\tilde{\pi}_h/dt$ where $\tilde{\pi} = \tilde{\pi}_h + \tilde{\pi}_y + \tilde{\pi}_z$. Therefore, the governing equations for the translated system are given by

$$\begin{aligned}
\frac{d\tilde{\pi}}{dt} &= \lambda(1-\phi)(1-\pi_h^*-\pi_y^*-\pi_z^*)(\alpha_h\tilde{\beta}_h + \alpha_y\tilde{\beta}_y) - \mu\tilde{\pi} \\
&\quad - \lambda(1-\phi)(\alpha_h\beta_h + \alpha_y\beta_y)\tilde{\pi} - (\sigma\delta - \sigma\alpha\delta)(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z) + \sigma(1-\alpha)f(t), \\
\frac{d\tilde{\pi}_y}{dt} &= \sigma(1-\delta)(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z) - \mu\tilde{\pi}_y + \sigma f(t), \\
\frac{d\tilde{\pi}_z}{dt} &= \sigma\alpha\delta(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z) - \mu\tilde{\pi}_z - \sigma\alpha f(t), \\
\frac{d\tilde{\beta}_h}{dt} &= \lambda\gamma(\tilde{\pi} - \tilde{\pi}_y - \tilde{\pi}_z - \tilde{\beta}_h) - \tau\tilde{\beta}_h, \\
\frac{d\tilde{\beta}_y}{dt} &= \lambda\gamma(\tilde{\pi}_y - \tilde{\beta}_y) - \tau\tilde{\beta}_y.
\end{aligned}$$

We can write this system in matrix form giving

$$\frac{d\tilde{\boldsymbol{y}}}{dt} = \mathbf{W}(\boldsymbol{y})\tilde{\boldsymbol{y}} + \boldsymbol{f}_{\boldsymbol{y}},$$

where $\mathbf{W}(\boldsymbol{y})$ is the matrix we derived earlier and $\boldsymbol{f}_{\boldsymbol{y}}^T = (\sigma(1-\alpha)f, \sigma f, -\sigma\alpha f, 0, 0)$. Since the matrix $\mathbf{W}(\boldsymbol{y})$ remains unchanged, the properties shown earlier still hold. Therefore, we can replace the β terms in the (1,1) position by a constant lower bound ϵ to obtain the matrix $\mathbf{W}^+$, where the eigenvalues of this matrix have strictly negative real parts. Hence there exists a symmetric positive definite matrix $\mathbf{P}$ such that

$$\mathbf{W}^+\mathbf{P} + \mathbf{P}\mathbf{W}^{+^T} = -\mathbf{Q}, \tag{3.64}$$

where $\mathbf{Q}$ is a positive definite matrix. If $\mathbf{P}$ is of the form

$$\begin{bmatrix} P_{11} & 0 & 0 & 0 & 0 \\ 0 & P_{22} & P_{23} & P_{24} & P_{25} \\ 0 & P_{32} & P_{33} & P_{34} & P_{35} \\ 0 & P_{42} & P_{43} & P_{44} & P_{45} \\ 0 & P_{52} & P_{53} & P_{54} & P_{55} \end{bmatrix},$$

where P_{11} is strictly positive, then we can prove global stability. Assuming that $\mathbf{P}$ is of the above form, $v = \tilde{\boldsymbol{y}}^T \mathbf{P} \tilde{\boldsymbol{y}}$ is a Lyapunov function for our system of equations, since v is always positive and

$$\begin{aligned} \frac{dv}{dt} &= \frac{d\tilde{\boldsymbol{y}}^T}{dt}\mathbf{P}\tilde{\boldsymbol{y}} + \tilde{\boldsymbol{y}}^T\mathbf{P}\frac{d\tilde{\boldsymbol{y}}}{dt}, \\ &\leq \tilde{\boldsymbol{y}}^T(\mathbf{W}^{+^T}\mathbf{P} + \mathbf{P}\mathbf{W}^+)\tilde{\boldsymbol{y}} + 2\tilde{\boldsymbol{y}}^T\mathbf{P}\boldsymbol{f}_{\boldsymbol{y}}, \\ &= -\tilde{\boldsymbol{y}}^T\mathbf{Q}\tilde{\boldsymbol{y}} + 2\tilde{\boldsymbol{y}}^T\mathbf{P}\boldsymbol{f}_{\boldsymbol{y}}. \end{aligned} \tag{3.65}$$

The Lyapunov function is related to the physical characteristics of our system. The idea of the proof is that the first term in (3.65) is negative and the second term becomes very small. We examine the $-\tilde{\boldsymbol{y}}^T\mathbf{Q}\tilde{\boldsymbol{y}}$ term in (3.65) first.

$$-\tilde{\boldsymbol{y}}^T\mathbf{Q}\tilde{\boldsymbol{y}} \leq -\omega_{\min}(\mathbf{Q})|\tilde{\boldsymbol{y}}|^2,$$

where $\omega_{\min}(\mathbf{Q})$ denotes the smallest strictly positive eigenvector of the positive definite matrix $\mathbf{Q}$. Since

$$\begin{aligned} |\tilde{\boldsymbol{y}}|^2 &\geq \frac{1}{\omega_{\max}(\mathbf{P})}\tilde{\boldsymbol{y}}^T\mathbf{P}\tilde{\boldsymbol{y}}, \\ &= \frac{1}{\omega_{\max}(\mathbf{P})}v \end{aligned} \tag{3.66}$$

where $\omega_{\max}(\mathbf{P})$ denotes the maximum strictly positive eigenvector of $\mathbf{P}$ we obtain

$$\begin{aligned} -\tilde{\boldsymbol{y}}^T\mathbf{Q}\tilde{\boldsymbol{y}} &\leq -\frac{\omega_{\min}(\mathbf{Q})}{\omega_{\max}(\mathbf{P})}v, \\ &= -kv, \qquad \text{where } k = \frac{\omega_{\min}(\mathbf{Q})}{\omega_{\max}(\mathbf{P})} > 0. \end{aligned}$$

We now examine the $\tilde{\boldsymbol{y}}^T \mathbf{P} \boldsymbol{f}_{\boldsymbol{y}}$ term in (3.65). The elements of the vector $\tilde{\boldsymbol{y}}$ are terms like $\tilde{\pi}_h = \pi_h - \pi_h^*$ and $\tilde{\beta}_h = \beta_h - \beta_h^*$ so $|y_i| \leq 1 \; \forall i$ and hence $|\tilde{\boldsymbol{y}}^T| \leq \sqrt{5}$. Now

$$|\tilde{\boldsymbol{y}}^T \mathbf{P} \boldsymbol{f}_{\boldsymbol{y}}| \leq |\tilde{\boldsymbol{y}}^T| \, ||\mathbf{P}|| \, |\boldsymbol{f}_{\boldsymbol{y}}|,$$

where $||\mathbf{P}|| < \infty$ denotes the matrix norm of $\mathbf{P}$ and

$$|\boldsymbol{f}_{\boldsymbol{y}}| < \sigma(1-\alpha)|f| + \sigma|f| + \sigma\alpha|f| = 2\sigma|f|.$$

This implies that $|\tilde{\boldsymbol{y}}^T \mathbf{P} \boldsymbol{f}_{\boldsymbol{y}}| < c|f(t)|$, where c is a constant. So as $t \to \infty$ the term $|\tilde{\boldsymbol{y}}^T \mathbf{P} \boldsymbol{f}_{\boldsymbol{y}}| \to 0$ and hence given $\epsilon_1 > 0$ we can choose $t_0 > 0$ such that for all $t \geq t_0$

$$|\tilde{\boldsymbol{y}}^T \mathbf{P} \boldsymbol{f}_{\boldsymbol{y}}| \leq \frac{\epsilon_1 k}{2}.$$

Therefore, for $t \geq t_0$

$$\frac{dv}{dt} \leq -kv + \frac{\epsilon_1 k}{2}.$$

From this we have

$$\frac{d}{dt}\left(v\exp(kt)\right) \leq \frac{\epsilon_1 k}{2}\exp(kt)$$

and integrating over $[t_0, t]$ gives

$$v \leq v(t_0)\exp(-k(t-t_0)) + \frac{\epsilon_1}{2}.$$

Now choose $t_1 \geq t_0$ such that for all $t \geq t_1$

$$v(t_0)\exp(-k(t-t_0)) \leq \frac{\epsilon_1}{2}.$$

Then for all $t \geq t_1$ $0 \leq v(t) \leq \epsilon_1$. Since ϵ_1 is arbitrary we deduce that $v(t) \to 0$

as $t \to \infty$. Furthermore, since

$$|\tilde{\boldsymbol{y}}|^2 \leq \frac{1}{\omega_{\min(\mathbf{P})}} \tilde{\boldsymbol{y}}^T \mathbf{P} \boldsymbol{y}$$

we deduce that $|\tilde{\boldsymbol{y}}| \to 0$ as $t \to \infty$. So provided that $R_0 > 1$, $\mathbf{P}$ is of the required form and the necessary condition proved earlier is satisfied the system of equations given by (3.59)-(3.63) tend to the endemic equilibrium as $t \to \infty$.

We now need to show that π_{h_1} and π_{h_2} both tend to their equilibrium values. Since $\pi_h \to \pi_h^*$ and $f(t) \to 0$ as $t \to \infty$ we can deduce that $\pi_{h_1} = (1-\delta)\pi_h + f(t) \to (1-\delta)\pi_h^*$ as $t \to \infty$. Performing an equilibrium analysis shows that $\pi_{h_1}^* = (1-\delta)\pi_h^*$. Similarly, $\pi_{h_2} = \delta\pi_h - f(t) \to \delta\pi_h^* = \pi_{h_2}^*$ as $t \to \infty$. Hence the system of equations given by (3.53)-(3.58) tend to the endemic equilibrium value as $t \to \infty$, provided that our conditions are satisfied. We now look at the equations

$$\frac{d\beta_{h_1}}{dt} = \lambda\gamma(\pi_{h_1} - \beta_{h_1}) - \beta_{h_1}\tau, \tag{3.67}$$

$$\frac{d\beta_{h_2}}{dt} = \lambda\gamma(\pi_{h_2} - \beta_{h_2}) - \beta_{h_2}\tau, \tag{3.68}$$

from the full system. Given an $\epsilon > 0$ there exists t_1 such that for all $t \geq t_1$ $\pi_{h_1} \leq \pi_{h_1}^* + \epsilon$. From (3.67) we have

$$\frac{d}{dt}\left(\beta_{h_1}\exp[(\lambda\gamma+\tau)t]\right) \leq \lambda\gamma(\pi_{h_1}^* + \epsilon)\exp[(\lambda\gamma+\tau)t].$$

Integrating over $[t_1, t]$ gives

$$\beta_{h_1} \leq \beta_{h_1}(t_1)\exp[-(\lambda\gamma+\tau)(t-t_1)] + \frac{\lambda\gamma(\pi_{h_1}^*+\epsilon)}{\lambda\gamma+\tau}\left(1 - \exp[-(\lambda\gamma+\tau)(t-t_1)]\right).$$

Choosing t_2 large enough so that $\exp\left[-(\lambda\gamma+\tau)(t-t_1)\right] \leq \epsilon$ for $t \geq t_2$ we deduce that

$$\beta_{h_1} \leq \frac{\lambda\gamma}{\lambda\gamma+\tau}\pi_{h_1}^* + \hat{\epsilon}, \qquad \forall t \geq t_2 > t_1, \text{ where } \hat{\epsilon} = \frac{\lambda\gamma}{\lambda\gamma+\tau}\epsilon + \epsilon.$$

Hence,

$$\limsup_{t\to\infty} \beta_{h_1} \leq \frac{\lambda\gamma}{\lambda\gamma+\tau}\pi^*_{h_1} + \hat{\epsilon}$$

and similarly we can show that

$$\liminf_{t\to\infty} \beta_{h_1} \geq \frac{\lambda\gamma}{\lambda\gamma+\tau}\pi^*_{h_1} - \hat{\epsilon}.$$

Since ϵ is arbitrary we can let $\epsilon \to 0$, and deduce that

$$\liminf_{t\to\infty} \beta_{h_1} = \limsup_{t\to\infty} \beta_{h_1} = \frac{\lambda\gamma}{\lambda\gamma+\tau}\pi^*_{h_1} = \beta^*_{h_1},$$

and so $\beta_{h_1} \to \beta^*_{h_1}$ as $t \to \infty$. Similarly, $\beta_{h_2} \to \beta^*_{h_2}$ as $t \to \infty$. Therefore, provided that the sufficient conditions for the five dimensional system are met, the seven dimensional system is globally stable. Then, since all infectious classes tend to their equilibrium values, we can deduce that the susceptible x and x_1 classes must also tend to their equilibrium values. Therefore, provided the conditions are satisfied, our model given by equations (3.1)-(3.9) will be globally stable, in the sense that provided the system starts away from the DFE and $R_0 > 1$ it will approach the unique endemic equilibrium.

3.6 Conclusion

In this chapter we have developed a model to approximate HCV transmission among Glasgow IDUs, building on the models developed by Vickerman *et al.* (2007). We have shown analytically that the behaviour of the model is governed by the basic reproductive number R_0, with $R_0 = 1$ a critical threshold for endemic HCV prevalence. We have shown that if $R_0 \leq 1$ and the disease is initially present in the population, then the system will tend toward the globally stable DFE where HCV has been eliminated in all IDUs and needles. If $R_0 > 1$ we have shown that HCV will be persistent in our population and that there is a unique endemic equilibrium. For a realistic approximation to the basic model this unique endemic equilibrium is locally stable. Furthermore, we have found

that provided $R_0 > 1$ and HCV is initially present in the population, our model will tend towards the endemic equilibrium, provided that certain conditions are satisfied.

This concludes the formal analysis of this simple model. In the next chapter we shall describe numerical simulations using this simple HCV transmission model. After a detailed discussion of our parameter estimates we determine both analytically and numerically the threshold values that, when reached, result in HCV elimination in our IDU population. We then examine how the uncertainty in some biological parameter estimates affects our estimates of HCV prevalence and how different situations affect the behaviour of our model.

Chapter 4

Simple HCV transmission model: Parameter estimation and numerical simulations

In 2004, the Scottish Government recognised that "Hepatitis C (HCV) is one of the most serious and significant public health risks of our generation". In recognition of this significant public health issue, the Scottish Government launched its Hepatitis C Action Plan in September 2006. One of its main aims is to prevent the spread of HCV, particularly among IDUs. Services providing needle and syringes to IDUs in Scotland have been developed since the late 1980s; and these have been highly effective in preventing the transmission of HIV among IDUs in Scotland. However, the incidence and prevalence of HCV (a more infectious virus than HIV) among IDUs remains high. Glasgow (the largest city in Scotland) has one of the highest prevalences of injecting drug use and HCV infection among IDUs in Europe; of an estimated 9,000 current IDUs in Glasgow approximately 70% have been infected with HCV (NESI 2010). Here we use the simulation package Berkeley Madonna version 8.3.11 (Macey *et al.* 2000) to produce HCV prevalence estimates for the Glasgow IDU population over time given by our model governing equations with the following aims:

1. Determine R_0 on the basis of available parameter estimates.

2. Examine the impact of various parameter estimates on R_0, in particular determine the threshold values of needle sharing (λ), needle cleaning (ϕ)

and needle turnover (τ) that lead to $R_0 \leq 1$ and eventual HCV elimination in our population.

Therefore, we need estimates for biological parameters such as the probability of disease transmission through needles and syringes, as well as behavioural parameters such as needle and syringe sharing rates. Since there does not seem to be a standard set of parameter values relating to the behaviour of IDUs and the biological properties of HCV, we discuss the various biological and behavioural parameter estimates found in the literature, as well as those obtained from IDU survey data provided by HPS. The parameter estimates selected for use in our simulations will then be highlighted along with the reasons behind their selection. Our simulation results then follow.

4.1 Behavioural parameters

Table 4.1 summarises the behavioural parameter estimates published in the literature, as well as unpublished data obtained from observational studies for the purpose of this analysis.

4.1.1 Probability of successful needle cleaning (ϕ)

In the past, successful cleaning in relation to preventing HIV transmission has been interpreted by experts as IDUs must always clean equipment with bleach, alcohol or boiling water (Goldberg *et al.* 1995). A number of HIV modelling papers contain significantly varying estimates for ϕ. It is unclear however whether successful needle cleaning for HIV is equivalent to successful needle cleaning for HCV. Here, we define and make assumptions on successful needle cleaning in relation to HCV.

Work has previously been published on needle cleaning with bleach and HIV (Abdala *et al.* 2001, 2004), and this group is currently working on needle cleaning and HCV. A short documentary found on the Harm Reduction Works website (National Treatment Agency 2009) talks to the research team who conducted laboratory experiments on HIV and cleaning practices. This documentary suggests that cleaning needles and syringes with water and bleach will kill all blood borne infections in more than 99% of syringes, while washing with soaps, water or

Estimate	Source	Notes
(a) Probability of successful needle cleaning (ϕ)		
0.84	Kaplan and O'Keefe (1993)	Observed data on American IDUs during 1990-1991
0.442	Goldberg *et al.* (1995)	Observed data on Glasgow IDUs during 1990
0.64	Greenhalgh and Lewis (2000, 2002)	Average of Goldberg *et al.* (1995) and Kaplan and O'Keefe (1993)
0.793	Vickerman *et al.* (2009)	Observed data on Pakistani IDUs (period not reported)
0.5	Murray *et al.* (2003)	Observed data on Australian IDUs during 1994
0.255	Unpublished data HPS Observed (1990-1993)	Observational data on Glasgow IDUs during 1990-1993
(b) Needle and syringe sharing rate (λ) per year: for needle and syringe sharing IDUs		
171	Greenhalgh (1997)	Observed data on Glasgow IDUs during 1990
192	Vickerman *et al.* (2007)	Observed data on London IDUs during 2000-2001
103	Unpublished data HPS (1990-1993)	Observed data on Glasgow IDUs during 1990-1993
19	Unpublished data HPS (2007)	Observed data on Glasgow IDUs during 2007
(b) Needle and syringe sharing rate (λ) per year: for current IDUs		
72.48	Goldberg *et al.* (1995)	Observed data on Glasgow IDUs during 1990
34	Unpublished data HPS (1990-1993)	Observed data on Glasgow IDUs during 1990-1993
3	Unpublished data HPS (2007)	Observed data on Glasgow IDUs during 2007
246.18	Kaplan and O'Keefe (1993)	Observed data on American IDUs during 1990-1991
(c) Needle turnover rate (τ) per year		
15.53	Kaplan (1995)	Observed data on American IDUs during 1990-1992
133	Griesbach *et al.* (2006); King *et al.* (2009)	Observed data on N/S distribution during 2004-2005; Posterior mean estimates for Glasgow during 2003
(d) IDU to needle ratio (γ)		
0.1675	Kaplan and O'Keefe (1993)	Observed data on American IDUs from during 1990-1991
0.908	Greenhalgh and Lewis (2000, 2002)	Calculated from modelled estimates
1.002	Griesbach *et al.* (2006); King *et al.* (2009)	Observed data for Glasgow during 2004-2005; Posterior mean estimate for Glasgow during 2003
(e) Rate that IDUs leave the IDU population (μ) per year		
0.1	Kaplan and O'Keefe (1993) Vickerman *et al.* (2007)	Assumption based on disease incubation time
0.17	Hutchinson, Bird *et al.* (2006)	Modelled estimates for Glasgow IDUs in 2000
0.05	Murray *et al.* (2003)	Assumption for Australian IDUs
0.1333	Caulkins and Kaplan (1991)	Observational data on American IDUs during 1980s
0.125	Greenhalgh and Hay (1997)	Assumption based on mean incubation time for AIDS

Table 4.1: Summary of behavioural parameter estimates published in the literature and unpublished data obtained from observational studies.

alcohol was successful in approximately 85% of syringes. We have therefore assumed that the techniques used to successfully disinfect a needle and syringe contaminated with HIV will also disinfect one contaminated with HCV. Hence previously applied HIV model estimates for ϕ may also be relevant to HCV models.

HIV model estimates for ϕ range from 0.442 (Goldberg *et al.* 1995) to 0.84 (Kaplan and O'Keefe 1993). Goldberg *et al.* obtained their estimate from a survey of drug users in Glasgow. Their estimate is much lower than that obtained by Kaplan and O'Keefe from the New Haven needle exchange program. This higher estimate could be attributed to the data used by Kaplan coming from a formal needle exchange program where packets of bleach are dispensed and where IDUs are educated how to clean needles. Both estimates are subject to the errors inherent in self-reporting of risk behaviour by IDUs, however the sensitivity analysis of Kaplan and O'Keefe showed that their model was robust with this parameter estimate, but the model results were consistent with ϕ in the range 0.42-0.84. Greenhalgh and Lewis (2000, 2002) estimate $\phi = 0.64$ by taking the average of the Goldberg *et al.* and Kaplan and O'Keefe estimates.

From a study modelling HIV and HCV among IDUs, Murray *et al.* (2003) estimate $\phi = 0.5$ which corresponds to the fraction of needles cleaned before use in 1994. More recently Vickerman *et al.* (2009) estimate that the proportion of IDUs that cleaned their syringe the last time they shared is 79.3% with a 95% confidence interval of 73.1-84.7%, however it is not clear if this cleaning process is successful and if the behavioural characteristics in Rawalpindi, where the drug users in this survey are situated, are applicable to IDUs in other parts of the world.

We can also use IDU survey data collected by HPS (Hutchinson *et al.* 2000) during the early 1990s to estimate ϕ; surveys conducted since then have not asked about needle cleaning. From a total of 2,058 IDUs 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. Of the remaining 679 IDUs, the majority (91%, 620/679) reported that they always cleaned their needles before use (155 bleach, 15 alcohol, 105 boiling water, 345 other); 24 mostly cleaned their needles (5 bleach, 3 boiling water, 16 other), 8 cleaned about half the time (2 bleach, 6 other), 11 cleaned occasionally

(1 bleach, 10 other), 14 never cleaned and the remaining 2 said they did not know.

Utilising this HPS data from 1990-1993, we assumed that cleaning with bleach is 99.9% effective and alcohol is 85% effective at disinfecting needles and syringes infected with HCV (National Treatment Agency 2009); other methods were assumed completely ineffective. We also assumed that those individuals who mostly clean used needles prior to use will do this on average 87% of the time, those who clean about half the time will do so 50% of the time, and those who occasionally clean will do so on average 13% of the time. We assumed that the few individuals who reported that they did not know were completely ineffective at cleaning their needles before use. Applying these assumptions, we estimate that 173 of 679 (25.5%) IDUs, who reported sharing needles and syringes, would have cleaned their needles successfully the last time they injected, providing an estimate for ϕ of 0.255.

4.1.2 Needle and syringe sharing rate (λ)

As in our model, the Kaplan and O'Keefe (Kaplan and O'Keefe 1993) model assumes homogeneous sharing rates. Although this is in contrast to what has been observed in the IDU population, this assumption is made for simplicity. Kaplan and O'Keefe (1993) estimate that, for the New Haven needle exchange program, $\lambda = 246.18$ shared injections per year, an estimate that is also used by Greenhalgh and Lewis (2000, 2002) in their simulations.

Goldberg *et al.* (1995) suggest a mean shared injection rate for Glasgow IDUs of 72.48 events per year. The authors report, however, that the distribution for needle sharing is highly skewed with many IDUs not sharing at all, while a small number report sharing 900-1,800 times a year. Taking the data from Goldberg *et al.* (1995) and confining it to those that share, gives an average number of shared injections $\lambda = 171$ per year for those IDUs who report sharing (Greenhalgh 1997).

While modelling HCV transmission in London, Vickerman *et al.* (2007) estimate that the frequency of syringe sharing is approximately 16 shared injections per month. Assuming this rate remains constant we obtain an approximate value of $\lambda = 12 \times 16 = 192$ shared injections per year for IDUs who share needles and syringes.

Estimates for λ were also obtained from survey data of IDUs from Glasgow during 1990-1993 and 2007. Among a total of 2,058 IDUs surveyed in 1990-1993, 672 (33%) IDUs reported sharing needles and syringes and the frequency of sharing in the six month period prior to interview. The estimated number of shared needle and syringe injections was 69,222 per year for the 672 IDUs who had shared needles, giving an average shared injection rate of 103 sharing events per needle and syringe sharing IDU per year, or 34 sharing events per current IDU per year. Similarly, among a total of 361 Greater Glasgow and Clyde IDUs surveyed in 2007, 62 (17%) IDUs reported sharing needles and syringes and the frequency of sharing in the six month period prior to interview. The estimated number of shared needle and syringe injections was 576 (range 486-756), giving an average shared injection rate of 19 (range 15.6-24.4) sharing events per needle and syringe sharing IDU per year, or 3 (range 2.6-4.2) sharing events per current IDU per year.

4.1.3 Needle turnover rate (τ)

This parameter represents the average number of needles and syringes that an IDU will turnover in one year.

Kaplan and O'Keefe (1993) assumed that needles will circulate indefinitely when there is no needle exchange present. This assumption is unrealistic since needles must have a limited working lifetime. In contrast, Kaplan (1995) uses data collected from the New Haven exchange project and estimates the natural needle turnover rate. This is defined as the rate at which needles are turned over in absence of a formal needle exchange program. Kaplan 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, an estimate also used by Greenhalgh and Lewis (2000, 2002) in their HIV modelling work.

Another, more recent, estimate for the needle turnover rate (τ) was generated by combining data on the size of the injecting population with survey data on the frequency of injecting and needle and syringe distribution. From a survey of 362 current IDUs in Greater Glasgow and Clyde in 2007, we estimated that there were a total of 213,964 injecting events that year for this group, generating an average of 591 injections per year per IDU. King *et al.* (2009) estimated that there were

7,918 current IDUs in the Greater Glasgow area in 2003. Assuming that these 7,918 Glasgow IDUs inject with needles and syringes at the same rate as those surveyed in 2007, then there were an estimated 4,679,538 injections in 2003. From the Scottish Needle Exchange Survey (Griesbach *et al.* 2006) 1,049,770 needles and syringes were distributed in Glasgow during the financial year 2004-2005. Assuming that the distribution of needles and syringes was the same in 2003, we estimated that each needle was used approximately 4.46 times before it was exchanged. Furthermore, if we assume that IDUs in 2003 inject on average at the same rate as those surveyed in 2007 (591 times per year), then IDUs inject on average 1.62 times per day. Therefore, 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.

4.1.4 IDU to needle ratio (γ)

Using data from the New Haven needle exchange program collected between November 1990 to February 1991, Kaplan and O'Keefe (1993) estimate $\gamma = 0.1675$.

Kaplan (1995) estimates from an infectious needle model that the rate at which uncontaminated needles become contaminated with HIV is 0.3675 per day, and the rate at which contaminated needles will become uncontaminated is 0.1665 per day. Using these values along with other parameter estimates Greenhalgh and Lewis (2000) are able to derive an estimate for the IDU to needle ratio. The authors start with two equations; one which corresponds to an HIV infected IDU injecting with a randomly selected needle and syringe which is then left infectious and one which corresponds to an uninfected IDU injecting with a contaminated needle and syringe that has been cleaned prior to use, rendering it uncontaminated. Using their notation we have

$$\begin{aligned}(\lambda/365)\gamma\pi^* &= 0.3675,\\ (\lambda/365)\gamma(1-\pi^*)\phi &= 0.1665,\end{aligned}$$

where π^* denotes the equilibrium prevalence of HIV in the population. The

authors assume (from Kaplan (1995)) that the prevalence of HIV amongst IDUs prior to needle exchange interventions is approximately 0.6. Substituting this value, along with their estimate of $\lambda = 246.22$ per year into the first equation above, the authors estimate that γ, the IDU to needle ratio, is approximately 0.908. This estimate is greater than that used in Kaplan and O'Keefe (1993) and may be more accurate since the data in Kaplan (1995) is collected over a longer period, November 1990 to June 1992.

We can also use the survey data available to calculate γ. The Scottish Needle Exchange Survey (Griesbach *et al.* 2006) reported that 1,049,770 needles and syringes were distributed in Glasgow in the financial year 2004-2005. Using this we are able to calculate the number of needles that are in circulation in the population at any instant. If we assume that the number of needles are distributed at a constant daily rate then there are approximately 2,874.11 needles released into the population each day. Using 2003 survey data we estimated that needles are used for 2.75 days before they are exchanged. This means that at any instant there are an estimated $2{,}874.11 \times 2.75$ or 7,904 needles in circulation in our population. King *et al.* (2009) estimated that there were 7,918 current IDUs in the Greater Glasgow area in 2003. This allows us to estimate $\gamma = 7,918/7,904 = 1.002$. This means that there are approximately 1,002 IDUs for every 1,000 needles.

4.1.5 Rate that IDUs leave the IDU population (μ)

Kaplan and O'Keefe (1993) assume that the remaining time spent injecting drugs by a newly HIV infected IDU equals the incubation time of the disease. This assumption may not be entirely accurate since it does not take into account other reasons why IDUs may leave the population. They estimate that the average incubation time of HIV is approximately ten years giving a rate for μ of 0.1 IDUs per year. This value is also used by Vickerman *et al.* (2007) in their HCV model.

In their modelling work on HIV in IDUs, Greenhalgh and Hay (1997) use a value of $\mu = 0.25$ IDUs per year. This estimate takes into account reasons, both AIDS related and otherwise, why infected IDUs will cease their shared injecting behaviour. The authors assume that 0.125 IDUs per year will leave the population for non-HIV related reasons and 0.125 IDUs per year will leave the population

due to AIDS related factors.

Lewis and Greenhalgh (2001) explicitly model the two ways in which IDUs can leave the sharing, injecting population. IDUs can leave the needle sharing population for non-HIV related factors such as death, treatment, and relocation, or they can leave due to the development of AIDS. The parameter μ represents the rate of leaving the population for non-HIV related factors. In line with their other work on HIV modelling (Greenhalgh and Lewis 2000, 2002), the authors use the Caulkins and Kaplan (1991) estimate of $\mu = 0.1333$ IDUs per year.

It is reasonable to assume that IDUs 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. Therefore, the estimates of μ found in Greenhalgh and Hay (1997) and Lewis and Greenhalgh (2001), 0.125 IDUs per year and 0.1333 IDUs per year respectively, could be used for modelling HCV in an IDU population.

Similarly to Greenhalgh and Hay (1997) we can estimate μ for HCV related factors and non-HCV factors. The incubation time of HCV is approximately 30 years, therefore, IDUs would leave the population for HCV related reasons at a rate of 1/30 IDUs per year. If we assume that IDUs will leave the population at a rate of 0.125 IDUs per year for non-HCV related reasons we obtain an estimate of $\mu = 0.1583$ IDUs per year. Since the incubation time of the HCV is so long it is reasonable to assume that very few IDUs will stop sharing needles and syringes due to the effects of HCV infection and, as a result, we could estimate a rate of 0.125 IDUs per year for non-HCV related causes.

Murray *et al.* (2003) assume in their combined HCV and HIV model that the rate at which IDUs with HCV infection leave the population for any reason is 0.05 IDUs per year.

We estimated $\mu = 0.17$ IDUs per year based on modelled estimates from Hutchinson, Bird *et al.* (2006) which applied to Glasgow IDUs during the 2000s and accommodated mortality and cessation of injecting drug use.

4.2 Biological parameters

We now discuss the biological parameter estimates published in the literature. Table 4.2 summarises our findings:

Estimate	Source	Notes
(a) Acute HCV transmission probability† (α_h)		
0.015-0.05	Advisory Council on the Misuse of Drugs (2009)	Obtained from Vickerman *et al.* (2009) model fits to Pakistan prevalence data
0.015-0.14	Vickerman *et al.* (2009)	Obtained by collating information on transmission through needle stick injury and scaling up HIV transmission probabilities
0.2-0.3	Hutchinson, Bird *et al.* (2006)∗	Assumption based on knowledge for HIV
0.04	Murray *et al.* (2003)	Average HCV infections from hollow bore needle accidents
0.018-0.0432	Vickerman *et al.* (2007)	Obtained from model fits to seroprevalence data from London for 2003
0.013-0.049	Crofts *et al.* (1999)	Estimated from Australian prevalence and needle stick infection probability estimates
(b) Chronic HCV transmission probability† (α_y)		
0.015-0.05	Advisory Council on the Misuse of Drugs (2009)	Obtained from Vickerman *et al.* (2009) model fits to Pakistan prevalence data
0.015-0.14	Vickerman *et al.* (2009)	Obtained by collating information on transmission through needle stick injury and scaling up HIV transmission probabilities
0.02-0.03	Hutchinson, Bird *et al.* (2006)	Assumption based on observed data on HCV transmission through needle stick injury
0.04	Murray *et al.* (2003)	Average HCV infections from hollow bore needle accidents
0.016-0.043	Vickerman *et al.* (2007)	Obtained from model fits to seroprevalence data from London for 2003
0.013-0.049	Crofts *et al.* (1999)	Estimated from Australian prevalence and needle stick infection probability estimates
(c) Duration of acute HCV infection ($1/\sigma$)		
6-24 Weeks	Vickerman *et al.* (2007)	Observational data from studies on acute HCV
24 Weeks	Kamal (2008)	Review of studies on acute HCV from 1976-2007
3-24 Months	Vickerman *et al.* (2009)	Observational data from studies on acute HCV
(d) Proportion of IDUs that develop immunity to HCV re-infection (α)		
18-50%	Vickerman *et al.* (2007)	Assumption due to model structure
0-100%	Vickerman *et al.* (2009)	Assumption
0.278	Micallef *et al.* (2007)	Observational data on Australian IDUs from 1993-2002
(e) Proportion of IDUs that spontaneously resolve HCV infection (δ)		
18-50%	Vickerman *et al.* (2007)	Observational data from studies into spontaneous viral clearance
15-40%	Hutchinson, Bird *et al.* (2006)	Obtained from review article and longitudinal study of IDUs
26%	Micallef *et al.* (2006)	Review of longitudinal studies from 1980-2003
20-40%	Kamal (2008)	Review of studies on acute HCV from 1976-2007

*Transmission probability lasts for 6-8 weeks during the early acute phase of infection.
†per needle and syringe sharing act.

Table 4.2: Summary of biological parameter estimates published in the literature.

4.2.1 Acute and chronic HCV transmission probabilities (α_h, α_y)

For simplicity, most studies consider the probability of disease transmission per sharing act to be the same for both acute and chronic HCV infection. Murray *et al.* (2003) modelled the prevalence of HIV and HCV among IDUs in Australia. They estimate that the probability of contracting HCV after injecting with an infected needle is 4% and suggest that the bounds on HCV infectivity are 1.2-10%. Another Australian study of IDUs (Crofts *et al.* 1999) estimates that the probability of HCV infection associated with a single injection with a used needle of unknown infection status is 1.3-4.9%.

The Advisory Council on the Misuse of Drugs (2009) reports that the probability of becoming infected with HCV after using an infected syringe ranges from 1.5-5%. This estimate comes from work conducted by Vickerman *et al.* (2009) which assumes one transmission probability for both acute and chronic HCV infection ranging from 1.5-14%. Using different starting points in the parameter uncertainty range, the authors used a numerical algorithm to determine possible model fits to data from Rawalpindi, Pakistan. These model fits suggest a smaller transmission probability range of 1.5 to 5%.

Initial infection with HIV is followed by a period of high viraemia. Estimates for the infectivity of HIV at different stages of infection suggest that there is a ten-fold increase in infectivity during this high phase of viraemia. Although this knowledge does not exist for HCV, we can assume a similar behaviour to HIV; infectivity in the acute stage of infection is higher than the chronic stage of infection. This idea is explored by Hutchinson, Bird *et al.* (2006).

Using stochastic simulation, Hutchinson, Bird *et al.* (2006) model HCV spread amongst IDUs. They assume that the probability of becoming acutely infected with HCV after initial exposure is 2-3% (range 1-10%), and they explore the effect of a ten-fold increase in infectivity during the acute phase of infection which lasts for a period of six to eight weeks. This implies that for six to eight weeks acute HCV transmission probability is 20-30%, which falls to 2-3% for the rest of the acute phase of infection. The transmission probability for chronic HCV infection is also assumed to be 2-3%. Incorporating this ten-fold increase into the model produced HCV prevalences consistent with the observed study data.

Vickerman *et al.* (2007) assume a different probability for disease transmission for chronic and acute HCV while modelling the spread of HCV amongst IDUs 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 one to ten. Using different starting points in the parameter uncertainty range, the authors used a numerical algorithm to determine possible model fits to London seroprevalence data. The four best model fits 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. Although different transmission probabilities for the acute and chronic phase were initially assumed, the results indicate that good model fits can be achieved without this assumption.

4.2.2 Duration of acute HCV infection ($1/\sigma$)

The acute phase of infection refers to the first six months after initial infection (Hoofnagle 2002; Kamal 2008) where spontaneous viral clearance is possible. While modelling HCV transmission in London, Vickerman *et al.* (2007) estimate that the duration of the acute phase ranges from 6-24 weeks. Taking different starting points in the parameter uncertainty range, the authors used a numerical algorithm to determine possible model fits to London seroprevalence data.

While the majority of individuals spontaneously clear their HCV infection in this six month period, it has been documented that spontaneous viral clearance has occurred up to 24 months after initial infection (Cox *et al.* 2005; Larghi *et al.* 2002). In order to incorporate these individuals into their Pakistan HIV and HCV model Vickerman *et al.* (2009) estimate that the duration of the acute phase ranges from 3-24 months.

4.2.3 Proportion of IDUs that develop immunity to HCV re-infection (α)

This is one of the most difficult parameters to estimate as there is a large uncertainty surrounding the level of immunity gained from previous exposure to HCV.

Previous modelling work on HCV that has modelled an immune state includes Vickerman *et al.* (2007, 2009).

Vickerman *et al.* (2007) assume that a proportion of IDUs, ranging from 18-50%, are able to resolve their initial HCV infection and after a period of acute HCV infection all of these become immune for life. More realistically, 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 IDUs becoming susceptible again. Due to the large uncertainty in estimating this parameter Vickerman *et al.* (2009) estimate that the proportion of IDUs who become immune ranges from 0-100%. A numerical algorithm was used to obtain model fits from different starting points in the parameter uncertainty space, however, the actual values used in the best model fits are not known. Furthermore these values result from fitting to Pakistan data therefore they could be unsuitable for our model.

Some, but not all, studies have shown a lower rate of (re-)infection for HCV among previously infected compared to previously uninfected IDUs (Micallef *et al.* 2007; Aitken, Lewis *et al.* 2008). While this could be interpreted as evidence of immunity to HCV re-infection, it is difficult to quantify to what extent IDUs who have spontaneously resolved an HCV infection develop immunity to HCV re-infection based on these few studies with relatively short follow-up periods and small sample sizes.

4.2.4 Proportion of IDUs that spontaneously resolve HCV infection (δ)

Since the majority of acute HCV infections are asymptomatic and therefore go undiagnosed it can be difficult to accurately estimate the rate of spontaneous resolution. Hutchinson, Bird *et al.* (2006) assume that this proportion is in the range 15-40%, with a similar estimate of 18-50% used by Vickerman *et al.* (2007).

A systematic review of longitudinal studies involving 675 subjects suggests that 26% of individuals will spontaneously resolve their HCV infection (Micallef *et al.* (2006)). This estimate was used by Vickerman *et al.* (2009) in their most recent modelling work on HCV and HIV in Pakistan. While this estimate falls into the ranges used by both Hutchinson, Bird *et al.* (2006) and Vickerman *et al.* (2007), Micallef *et al.* report that this may be an under-estimate given the

limitations inherent in studies of acute HCV.

Furthermore, a systematic review of acute HCV by Kamal (2008) suggests that estimates of spontaneous viral clearance range from 10-60%. Although this is a wide range of estimates Kamal states that as a general rule of thumb approximately 20-40% of patients will spontaneously clear HCV infection.

4.3 Parameter estimates used for simulations

We now highlight the parameter estimates that have been selected for use in our simulations, along with the reasons behind their selection. Each parameter estimate was discussed with experts at HPS to ensure that the values selected were appropriate. It was our intention to use estimates gained from IDU survey data where possible, provided that those estimates are considered reasonable.

To gain information on the uptake of needle cleaning practices researchers rely on self-report questionnaires completed in health clinics and needle exchange settings. The reliability of the data supplied by IDUs in these settings could misrepresent the true risk behaviour in the population. If the model is used to estimate minimal elimination quantities, an under-estimate in needle cleaning will result in an over-estimate in the elimination quantities needed to eliminate the disease, thus ensuring success. IDU survey data from Glasgow provided us with an estimate of $\phi = 0.255$, which was the lowest estimate found. Therefore, we assumed that $\phi = 0.255$ in the simulations.

Since a small number of IDUs can share significantly more than others, one can assume that these IDUs can have a large effect on the spread of the disease (Greenhalgh 1997). As a result, it might be reasonable to apply needle sharing data from those who report needle and syringe sharing. Using survey data from Glasgow we assumed $\lambda = 103$ shared injections per year.

In reviewing the needle turnover rate we found two possible values. The value of $\tau = 15.53$ per year from Kaplan (1995) suggests a working life of 23.5 days per needle, a value that seems rather unrealistic given the injecting practices of some IDUs. The working life of 2.75 days obtained from Glasgow survey data implies a needle turnover rate of 133 per year and was used in the simulations.

The IDU to needle ratio estimate of $\gamma = 0.908$ used by Greenhalgh and Lewis (2000) and Greenhalgh and Lewis (2002) is much higher than the estimate of

$\gamma = 0.1675$ used by Kaplan and O'Keefe (1993). Greenhalgh and Lewis suggest that their estimate is more accurate than that of Kaplan and O'Keefe (1993) since the survey data used in Kaplan (1995) is collected over a longer period. Using HPS data we have been able to estimate that $\gamma = 1.002$. Since this estimate is calculated from more recent survey data we use this estimate.

A number of parameter estimates for μ were found in the literature. The estimate of $\mu = 0.1$ IDUs per year by Kaplan and O'Keefe (1993) is estimated from the incubation time of HIV. This estimate does not take into account other reasons why IDUs may leave the population. The estimate of $\mu = 0.17$ IDUs per year by Hutchinson, Bird *et al.* (2006) relating to Glasgow may be more accurate than the estimate of $\mu = 0.05$ IDUs per year which relates to the behaviour of Australian IDUs (Murray *et al.* 2003), and $\mu = 0.1333$ IDUs per year by Caulkins and Kaplan (1991) which comes from older survey data. Without a more rigorous method to estimate this parameter we assume that $\mu = 0.17$ IDUs per year.

We assumed that the infectivity of, and probability of HCV transmission associated with, acute HCV infection (α_h) was greater than that of chronic infection (α_y). Unlike Hutchinson, Bird *et al.* (2006), we do not explicitly model a six to eight week period of high viraemia. Instead we assumed that if this period of high viraemia was incorporated into a general acute phase lasting six months or longer, then the effects of this high transmission period will be averaged out, resulting in a transmission probability in line with other studies. We assumed that $\alpha_h = 0.0432$ and $\alpha_y = 0.016$, based on Vickerman *et al.* (2007).

The acute phase of infection was taken to be the first six months after initial infection (Vickerman *et al.* (2007, 2009)). Thus we estimated that $(1/\sigma) = 0.5$ years or $\sigma = 2$ per year.

Due to the uncertainty in estimating this parameter, Vickerman *et al.* (2009) estimated that the proportion of IDUs who become immune could range from 0-100%. Here, we have estimated conservatively that $\alpha = 0.25$.

Further, we assumed $\delta = 0.26$ based on a systematic review of longitudinal studies involving 675 subjects (Micallef *et al.* 2006).

Parameter	Definition	Estimate
ϕ	probability of successful needle cleaning	0.255
λ	needle and syringe sharing rate	103 per year
τ	needle turnover rate	133 per year
γ	IDU to needle ratio	1.002
μ	rate IDUs leave the sharing population	0.17 per year
α_h	acute HCV transmission probability	0.0432*
α_y	chronic HCV transmission probability	0.016*
$1/\sigma$	duration of the acute HCV phase	0.5 years
δ	proportion that resolve HCV infection	0.26
α	proportion of IDUs** that become immune	0.25

*per shared injection

**who have spontaneously resolved an HCV infection

Table 4.3: Table of parameter estimates used in simulations.

4.4 Simulation results

4.4.1 Determining R_0

Using the baseline set of parameter estimates given in Table 4.3 we estimated that $R_0 = 2.82 > 1$, which includes intervention measures such as needle exchange and needle cleaning. We simulate the transmission of HCV in our model when $R_0 = 2.82$ over a period of 70 years. Initially we assumed that 1% of our IDU population were infected with acute HCV (h_1) and no other IDUs or needles are infected. That is, $\pi_x(0) = 0.99$, $\pi_{x_1}(0) = 0$, $\pi_{h_1}(0) = 0.01$, $\pi_{h_2} = 0$, $\pi_y(0) = 0$, $\pi_z(0) = 0$, and $\beta_{h_1}(0) = \beta_{h_2}(0) = \beta_y(0) = 0$ where $\pi_x(0)$ denotes the fraction of IDUs in the x-susceptible class at time $t = 0$ and similarly for all other IDU and needle classes. The prevalence of HCV (we use the HPS definition of those testing HCV antibody positive, which is given by $\pi_{x_1} + \pi_{h_1} + \pi_{h_2} + \pi_y + \pi_z$) in the IDU population, as well as the infectious needles, are shown in Figure 4.1.

It is clear from Figure 4.1 that the fraction of IDUs and needles infected with HCV eventually reaches a steady state solution. The approximate steady state values for IDUs in each stage of infection are $(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.3107, 0.0439, 0.0456, 0.0160, 0.5366, 0.0471)$. Similarly, for needles at each stage of infection, the approximate steady state values are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*)$ =(0.0199, 0.0070, 0.2345). This corresponds to an endemic HCV prevalence of $\pi^* = 0.6892$

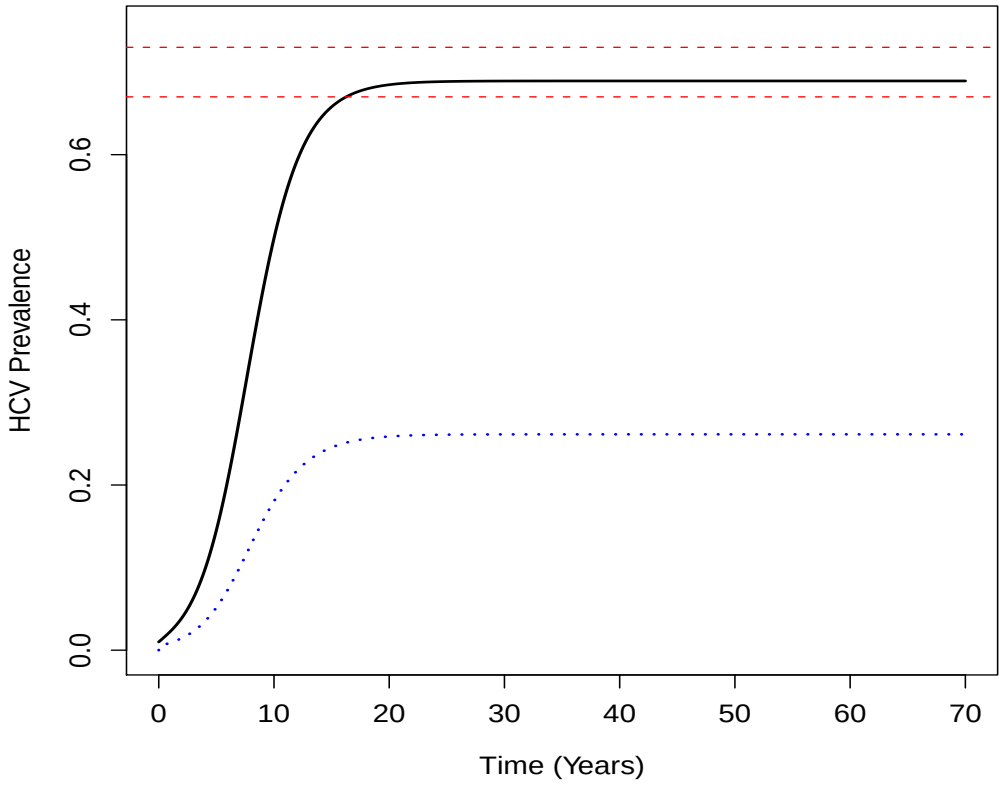

Figure 4.1: HCV prevalence among Glasgow needle and syringe sharing IDUs (solid black line) and infectious needles (dashed blue line) when $R_0 = 2.82$. The prevalence of HCV among Glasgow IDUs during 2008-2009 was observed to be 70% (95% CI 67-73%); the 95% confidence interval range is shown by the dashed red lines.

for needle and syringe sharing IDUs in Glasgow and $\beta^* = 0.2614$ for needles, where $\pi^* = \pi^*_{x_1} + \pi^*_{h_1} + \pi^*_{h_2} + \pi^*_y + \pi^*_z$ and $\beta^* = \beta^*_{h_1} + \beta^*_{h_2} + \beta^*_y$.

Further simulations were conducted using a range of initial conditions with the same limiting results. Figure 4.2 (a) and (b) are plots of long term HCV prevalence among IDUs and needles respectively varying the following initial conditions:

(i) $\pi_x(0) = 0.7$, $\pi_{h_1}(0) = 0.3$, $\beta_{h_1}(0) = 0$ with all other classes initially zero;

(ii) $\pi_x(0) = 0.3$, $\pi_{h_1}(0) = 0.7$, $\beta_{h_1}(0) = 0$ with all the other classes initially zero; and

(iii) $\pi_x(0) = 1$, $\pi_{h_1}(0) = 0$, $\beta_{h_1}(0) = 0.5$ with all other classes initially zero.

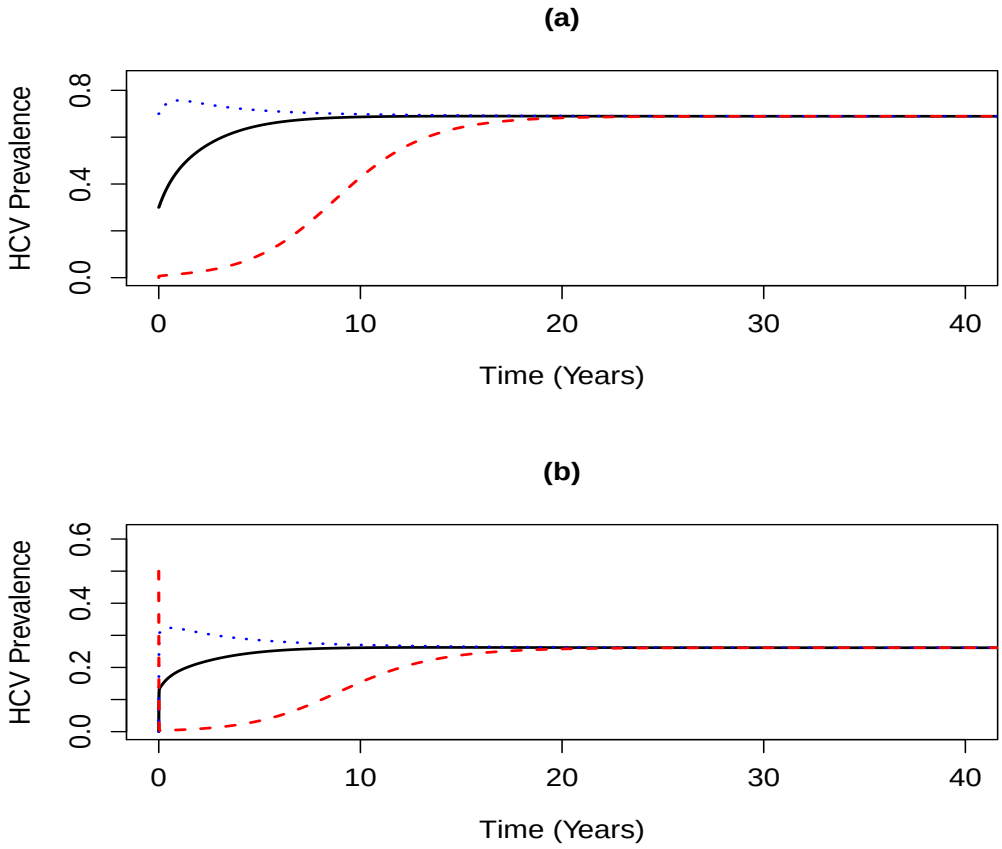

Figure 4.2: HCV prevalence among (a) Glasgow needle and syringe sharing IDUs and (b) infectious needles using initial conditions (i) (solid black line), (ii) (dotted blue line) and (iii) (red dashed line).

It is clear from Figure 4.2 that the prevalence of HCV among IDUs and needles reaches an equilibrium value which is independent of the initial conditions. Further examination confirms that the long term prevalence of HCV is 0.6892 for needle and syringe sharing IDUs and 0.2614 for needles. Furthermore, our extensive simulations, some of which are not shown, suggest that if HCV is initially present in the population, either in IDUs or needles, and $R_0 > 1$ then the model will tend to a unique equilibrium, as expected from Theorem 3.1.

4.5 Results for $R_0 \leq 1$

Analytical determination of critical values

Using equation (3.10) and Table 4.3, we were able to estimate values for each of λ, ϕ, and τ, keeping all other parameters fixed, that result in $R_0 = 1$ and therefore eliminate HCV.

Definition 4.1. *We define*

(i) λ_{crit} *to be the critical value of* λ *that results in* $R_0 \leq 1$ *if* $\lambda \leq \lambda_{crit}$*;*

(ii) ϕ_{crit} *to be the critical value of* ϕ *that results in* $R_0 \leq 1$ *if* $\phi \geq \phi_{crit}$*;*

(iii) τ_{crit} *to be the critical value of* τ *that results in* $R_0 \leq 1$ *if* $\tau \geq \tau_{crit}$*.*

4.5.1 Determining λ_{crit}

Earlier analysis of our simple HCV model confirms that, if $R_0 \leq 1$, the hepatitis C virus will die out in all IDUs and needles. Note that R_0 is a monotone increasing function of λ. In order to determine the critical value of λ necessary we start with the expression for R_0 derived in Chapter 3 with $R_0 = 1$ and $\lambda = \lambda_{crit}$. This gives

$$1 = \frac{\lambda_{crit}(1-\phi)}{\mu(\mu+\sigma)(1+\hat{\tau})}[\mu\alpha_h + \alpha_y\sigma(1-\delta)] \tag{4.1}$$

where $\hat{\tau} = \dfrac{\tau}{\lambda_{crit}\gamma}$.

After re-arranging and substituting in the expression for $\hat{\tau}$ we obtain

$$\lambda_{crit}^2 - \lambda_{crit}A - \frac{\tau}{\gamma}A = 0.$$

where $A = \dfrac{\mu(\mu+\sigma)}{(1-\phi)(\mu\alpha_h + \sigma(1-\delta)\alpha_y)}$. Solving we find that the unique positive root for λ_{crit} is

$$\lambda_{crit} = \frac{1}{2}\left(A + \sqrt{A^2 + \frac{4A\tau}{\gamma}}\right).$$

Substituting in the necessary parameter estimates from Table 4.3 then solving gives $\lambda_{crit} = 54.7$ per year. We conclude that a needle and syringe sharing rate of $\lambda \leq \lambda_{crit} = 54.7$ per year gives $R_0 \leq 1$ and therefore eventual HCV elimination in all IDUs and needles.

4.5.2 Determining ϕ_{crit}

We now wish to determine the level of successful needle and syringe cleaning that results in $R_0 \leq 1$ and HCV elimination in all IDUs and needles. We again start with the expression for R_0 but with ϕ replaced by ϕ_{crit}:

$$1 = \frac{\lambda(1-\phi_{crit})}{\mu(\mu+\sigma)(1+\hat{\tau})}[\mu\alpha_h + \alpha_y\sigma(1-\delta)] \tag{4.2}$$

where $\hat{\tau} = \dfrac{\tau}{\lambda\gamma}$.

Re-arranging (4.2) for ϕ_{crit} gives

$$\phi_{crit} = 1 - \frac{\mu(\mu+\sigma)(1+\hat{\tau})}{\lambda(\mu\alpha_h + \sigma(1-\delta)\alpha_y)}.$$

After substituting in the necessary parameter estimates from Table 4.3 we find that $\phi_{crit} = 0.736$. Therefore, we conclude that if the probability an IDU successfully cleans a needle prior to use $\phi \geq \phi_{crit} = 0.736$ then $R_0 \leq 1$ and HCV will die out in all IDUs and needles. This means that at least 74% of IDUs would need to successfully clean their needles and syringes before every use, provided no other parameters change.

4.5.3 Determining τ_{crit}

We are now going to perform a similar calculation to determine the average needle turnover rate that gives $R_0 \leq 1$. As before we begin with the derived expression for R_0 with $R_0 = 1$ and $\tau = \tau_{crit}$. This gives

$$1 = \frac{\lambda(1-\phi)}{\mu(\mu+\sigma)(1+\hat{\tau})}[\mu\alpha_h + \alpha_y\sigma(1-\delta)] \tag{4.3}$$

where $\hat{\tau} = \dfrac{\tau_{crit}}{\lambda\gamma}$.

Re-arranging (4.3) for τ_{crit} gives

$$\tau = \frac{\lambda^2\gamma(1-\phi)(\mu\alpha_h + \sigma(1-\delta)\alpha_y)}{\mu(\mu+\sigma)} - \lambda\gamma.$$

After substituting in the necessary parameter estimates from Table 4.3 we find that $\tau_{crit} = 562.82$ per year. Therefore, we conclude that if the needle turnover rate $\tau \geq \tau_{crit} = 562.82$ per year then $R_0 \leq 1$ and HCV will be eliminated in all IDUs and needles. The needle turnover rate used for our initial simulations suggested that the working life of a needle was approximately 2.75 days. To achieve $\tau_{crit} = 562.82$ per year, the working life of a needle would need to be reduced to 0.649 days, a figure that suggests a significant increase in needle distribution is needed. Assuming that IDUs continue to inject at the current rate of approximately 1.62 times per day, then every needle must be used 1.05 times before it is changed. If there are still 4,679,538 injections taking place per year then needle exchanges and health clinics would need to distribute approximately 4,456,702 needles to the IDU population each year, a substantial increase on the 1,049,770 needles currently distributed.

We have now been able to calculate the critical values of λ, ϕ, and τ that will result in HCV elimination in all IDUs and needles. These results are summarised in Table 4.4. We now use the software package Berkeley Madonna version 8.3.11 to verify our analytical results and to investigate how HCV prevalence estimates are affected by various parameter estimates.

	λ_{crit} (per year)	ϕ_{crit}	τ_{crit} (per year)
Estimate	54.7	0.736	562.82

Table 4.4: The critical values of λ, ϕ, and τ that result in $R_0 \leq 1$.

4.6 Intervention measures

We now numerically examine different scenarios that result in a reduction in R_0 so that $R_0 \leq 1$. To achieve this reduction we are going to focus on the levels of needle and syringe sharing (λ), successful needle cleaning (ϕ), and needle turnover (τ) that are needed to achieve the required value of R_0.

Firstly we will take each parameter individually and find the critical value required to reduce the value of R_0 so that HCV dies out in both IDUs and needles. Secondly, we combine all three parameters at their respective critical values and investigate what effect this has on disease elimination. Lastly, we will look at various pairs of parameters to find a range of estimates that would achieve HCV elimination in all IDUs and needles.

4.7 Using Berkeley Madonna to determine critical values

We begin by using the parameter plot command in Berkeley Madonna to obtain plots showing how the value of R_0 changes when we vary λ, ϕ, and τ independently. For each parameter we obtain a general parameter plot that shows its relationship with R_0. A further, more detailed plot is also obtained showing the parameter values that give rise to a value of R_0 close to one. These plots will allow us to estimate the critical values of λ, ϕ, and τ.

Figure 4.3 shows both the parameter and detailed plots for each parameter of interest. Figure 4.3 (a) and (b) show both plots of λ vs R_0, allowing us to estimate the critical value of λ that separates HCV persistence and elimination. In a similar way, Figure 4.3 (c) and (d) show the relationship between ϕ and R_0, while Figures 4.3 (e) and (f) show the relationship between τ and R_0.

From Figure 4.3 (b), (d), and (f) we are able to estimate λ_{crit}, ϕ_{crit}, and τ_{crit} the values of λ, ϕ, and τ respectively that separate our two kinds of model behaviour. Using Figure 4.3 we estimate that $\lambda_{crit} = 54.7$ per year, which is approximately equal to the value obtained analytically (see Table 4.4). Figure 4.3 (d) and (f) allow us to estimate that $\phi_{crit} = 0.736$ and $\tau_{crit} = 562.7$ per year respectively. These estimates are approximately equal to the values in Table 4.4 which were obtained analytically.

These simulations confirm our earlier analytical results and we can conclude that if either $\lambda \leq \lambda_{crit}$, $\phi \geq \phi_{crit}$, or $\tau \geq \tau_{crit}$ then $R_0 \leq 1$ and HCV will be eliminated in all IDUs and needles. Further simulations, which are not shown, were conducted to confirm this conclusion. These simulations showed that HCV elimination occurred when a single parameter reached its critical value, but since

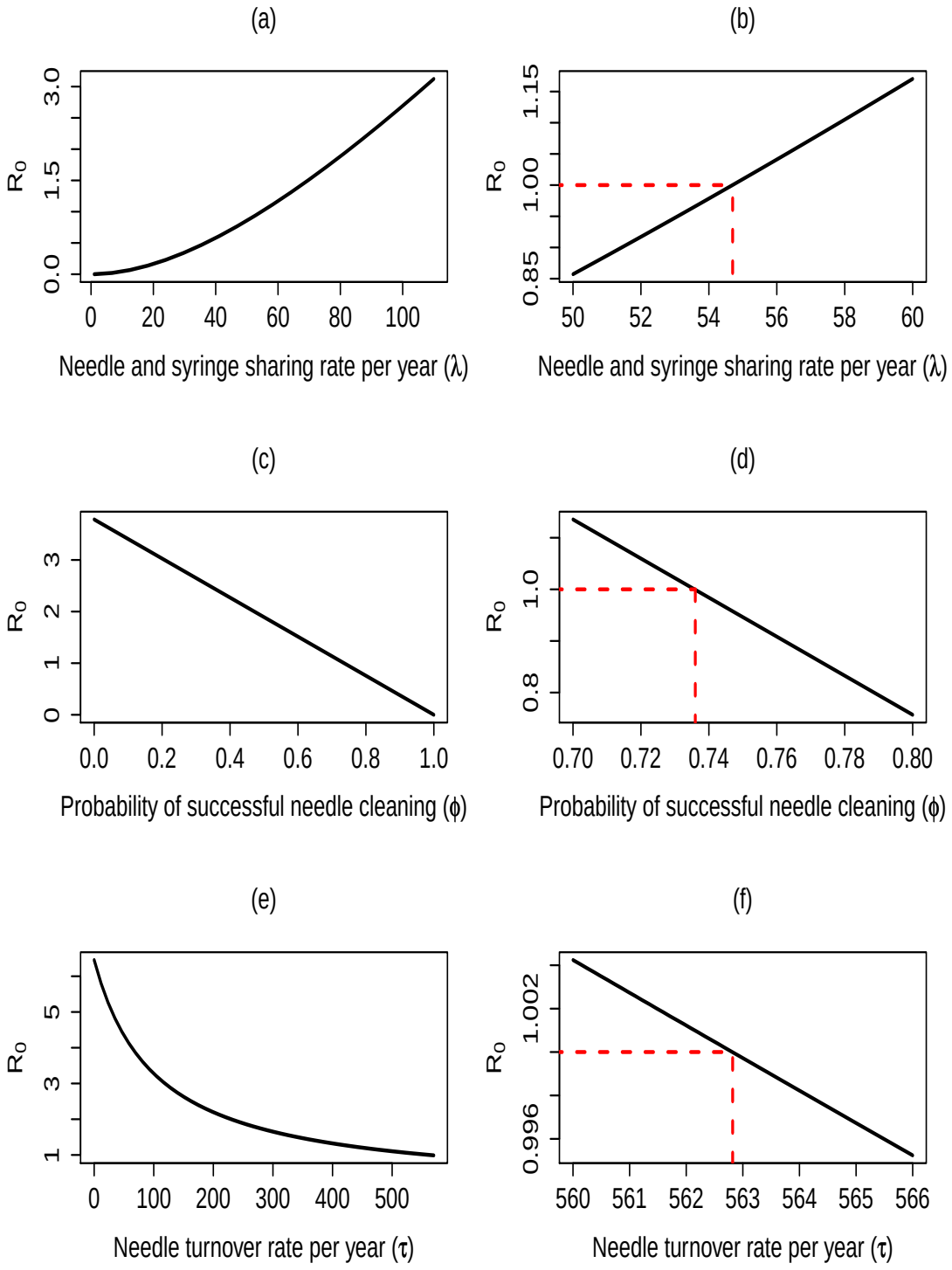

Figure 4.3: Parameter plots of λ , ϕ, and τ vs R_0. The critical value that separates HCV persistence and elimination for each parameter is indicated by the red dashed line.

R_0 is approximately one, the time taken to eliminate HCV in the population is very long.

In this section we have been able to find, both analytically and numerically, the critical values of λ, ϕ, and τ that result in HCV elimination in all IDUs and needles. Further simulations have shown that intervention measures targeted on a single parameter can eliminate HCV but the time taken for this process is considerable. It is therefore reasonable to assume that interventions targeting two or more parameters will achieve the same result in a shorter timeframe. This will be investigated in the next section.

4.8 Parameter combinations resulting in $R_0 \leq 1$

We have already seen that health organisations would need to distribute approximately 3.2 times more needles to IDUs to achieve the $R_0 = 1$ target, with significantly more needed to ensure that $R_0 < 1$. It is possible that a smaller increase in needle turnover combined with another parameter will result in IDUs and needles reaching a disease free state in a shorter time frame. In this section we focus on combining parameters and finding the range of values that allow for HCV elimination.

We begin by assuming that it has been possible to achieve λ_{crit}, ϕ_{crit}, and τ_{crit} using our intervention strategies. We then simulate our model behaviour using these values and evaluate the time taken for our system to reach a disease free state.

Figure 4.4 shows the resulting model behaviour when we combine these parameters. Initially we assume that 70% of IDUs are infected with HCV: 10% are in the acute h_1 stage of infection, 10% are in the acute h_2 stage of infection and 50% are in the chronic y stage of infection. That is, $\pi_x(0) = 0.3$, $\pi_{h_1}(0) = 0.1$, $\pi_{h_2}(0) = 0.1$, $\pi_y(0) = 0.5$ and $\pi_{x_1}(0) = \pi_z(0) = 0$. In addition, we assume that 30% of needles and syringes are infected with HCV with infection spread evenly among the three infectious needle classes. Hence $\beta_{h_1} = \beta_{h_2} = \beta_y = 0.1$. It comes as no surprise that HCV dies out in both IDUs and needles since we have used the three separate values necessary for disease elimination, resulting in $R_0 = 0.108$. The time taken for HCV elimination, however, is considerably shorter than our earlier simulations where intervention was focused on a single parameter. If these

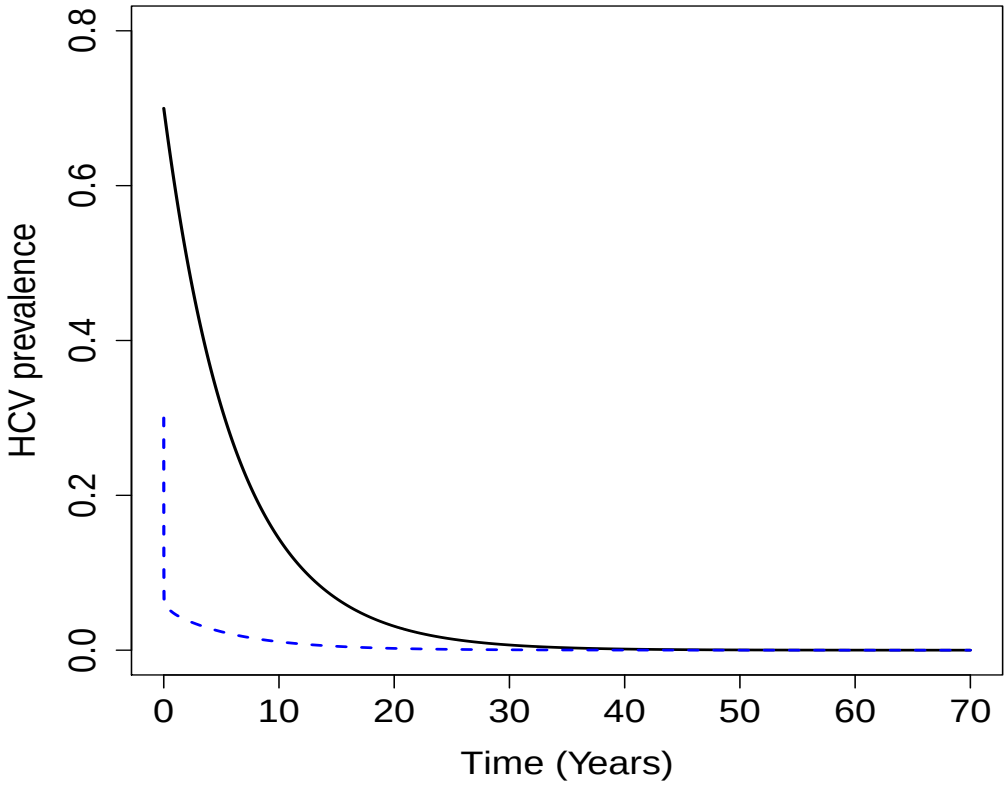

Figure 4.4: HCV prevalence among needle and syringe sharing IDUs (solid black line) and needles (dotted blue line) when $R_0 = 0.108 < 1$, $\lambda = 54.7$ per year, $\phi = 0.736$, $\tau = 562.82$ per year. Initially $\pi_x(0) = 0.3$, $\pi_{h_1}(0) = 0.1$, $\pi_{h_2}(0) = 0.1$, $\pi_y(0) = 0.5$, $\pi_{x_1} = \pi_z(0) = 0$ and $\beta_{h_1}(0) = \beta_{h_2}(0) = \beta_y(0) = 0.1$.

targets were achieved, Figure 4.4 shows that HCV elimination in our population is possible in approximately 40 years, a significant reduction on the very long timescale suggested by our earlier simulations. This indicates that intervention measures employed by health organisations must target key areas in order to obtain faster HCV elimination. We now use the software package Matlab 7.0.1 to investigate how the final value of R_0 changes as two parameters are altered simultaneously. We first define a suitable range of values for the two parameters of interest, with the remaining parameters taking the values specified in Table 4.3. Using the expression for R_0, equation (3.10), our Matlab program calculates the R_0 for all possible values in our parameter space. It then stores all the com-

binations that result in $R_0 \leq 1$ in a file which is then read into R 2.11.1 and plotted (Figure 4.5).

Figure 4.5 (a), (b), and (c) clearly show the combinations that will result in $R_0 \leq 1$ and eventual HCV elimination in all IDUs and all needles. Figure 4.5 (a) indicates the values of ϕ and τ that are needed to achieve an HCV free population. Similarly, Figure 4.5 (b) indicates the combinations of λ and ϕ that achieve the desired result, while Figure 4.5 (c) shows this for combinations of τ and λ. If the two parameters attain values that are contained in the grey shaded area then the resulting value of R_0 is less than or equal to one. If we assume that we have a needle and syringe sharing rate of 60 sharing events per needle and syringe sharing IDU per year, we can see from Figure 4.5 (b) and Figure 4.5 (c) that we would need a minimum successful cleaning probability of approximately 0.4 or a minimum needle turnover rate of approximately 150 per year to reduce R_0 to the desired level. This means that we would require the proportion of IDUs who successfully clean their needles and syringes before use to increase from 25.5% to 40% or the working life of a needle to decrease from 2.75 days to 2.44 days.

4.9 Examining the effect of various parameter estimates on HCV prevalence estimates

We have spent some time examining the values of λ, ϕ, and τ that would eliminate HCV in all IDUs and needles. From the previous two sections we can see that, while HCV elimination is possible, the level of intervention required to reach our critical values may be unrealistic, at least in the short to medium term.

In this section we will examine how more modest changes in the parameter estimates affect our estimates of HCV prevalence. HCV prevalence estimates will refer to IDUs who test positive for HCV antibodies, that is $\pi_{x_1}+\pi_{h_1}+\pi_{h_2}+\pi_y+\pi_z$, where x_1, h_1, h_2, y, and z denote the susceptible (previously infected), acute h_1, acute h_2, chronic and immune classes respectively. In some instances we will be interested in the effects our parameter estimates have on the number of infectious needles and syringes in our population. Intuitively, infectious needles and syringes are needles and syringes that are in either the acute or chronic stage of infection and the total number of these is given by $\beta_{h_1} + \beta_{h_2} + \beta_y$.

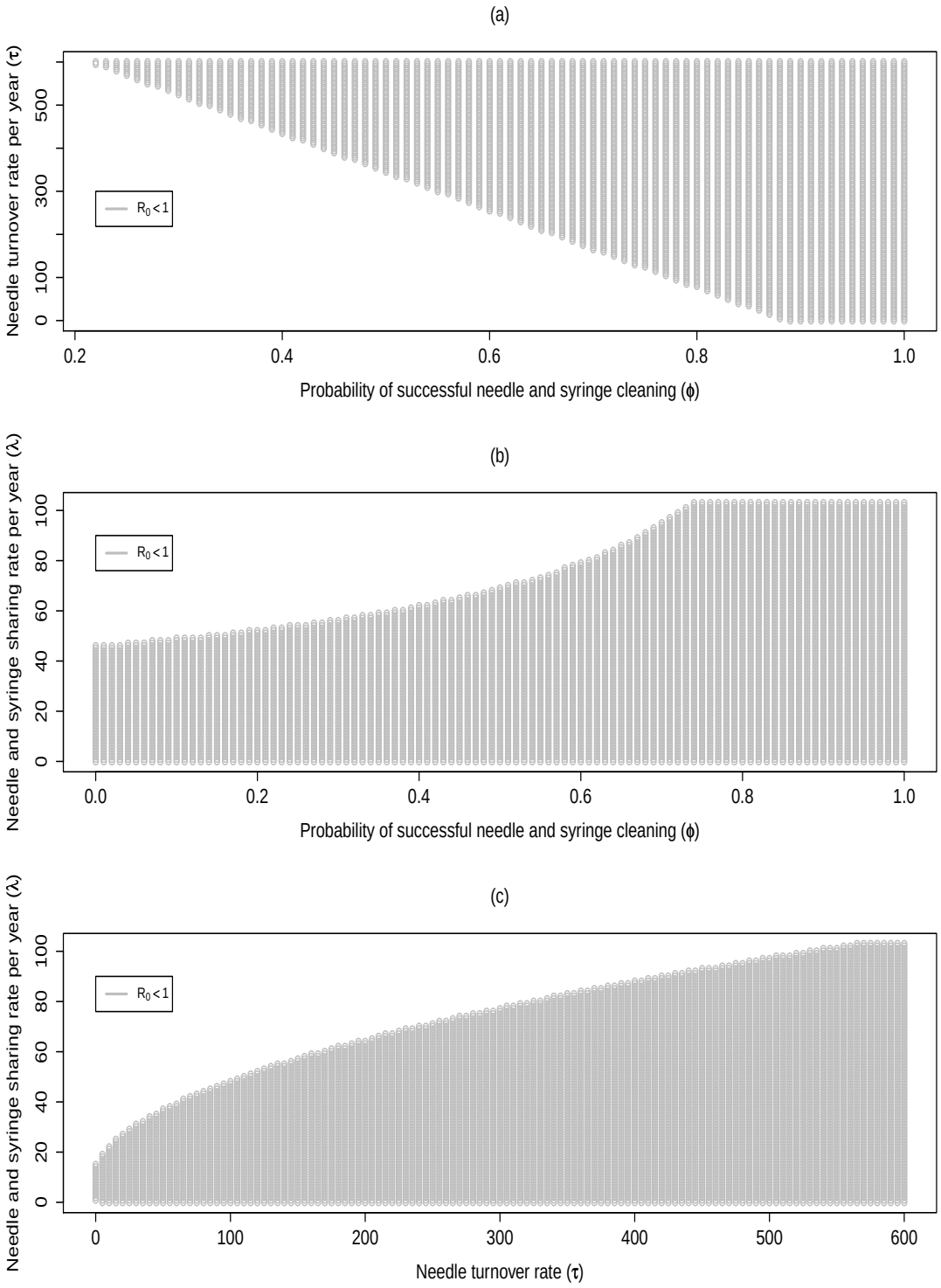

Figure 4.5: Plots showing the combinations of (a) ϕ and τ, (b) ϕ and λ and (c) τ and λ that result in $R_0 \leq 1$ (grey shaded area).

4.9.1 The effect of a 10% increase or decrease in sharing rates

We begin by investigating the effect changes in the needle and syringe sharing rate λ have on our long term estimates of HCV prevalence among IDUs and needles. Information about needle and syringe risk behaviour comes from self assessment questionnaires completed at needle exchanges or health clinics. The stigma attached to high risk behaviour in these settings could mean that IDUs give answers that are considered acceptable rather than divulge their true high risk behaviour. This calls into question the reliability of these data sources which modellers use for their parameter estimates.

The following set of simulations assesses how a 10% increase or decrease in our estimate of λ alters our endemic equilibrium prevalence of HCV. We run simulations using three different values of λ corresponding to our current parameter estimate ($\lambda = 103$ per year), a 10% increase in sharing rates ($\lambda = 113.3$ per year), and a 10% decrease in sharing rates ($\lambda = 92.7$ per year). Figure 4.6 shows the resulting HCV prevalence estimates for both IDUs and needles. To see the effects of these changes more clearly we have summarised the endemic equilibrium values for both groups of IDUs in Table 4.5.

λ (per year)	Prevalence among sharing IDUs	Prevalence among needles
92.7	0.629	0.222
103	0.689	0.261
113.3	0.735	0.296

Table 4.5: Endemic equilibrium HCV prevalence estimates for (a) sharing IDUs and (b) needles with needle and syringe sharing rates of $\lambda = 92.7, 103$ and 113.3 per year.

From these simulations we can see that increasing the needle and syringe sharing rate results in a more rapid increase in the number of infections and a greater endemic equilibrium prevalence. This result is not surprising since we are increasing both the value of R_0 and the main mode of HCV transmission in our population. Furthermore, we can see that decreasing needle and syringe sharing rates by 10% will result in a 6% reduction in long term IDU HCV prevalence and a 3.9% reduction in the proportion of infectious needles and syringes at equilibrium. We now use the parameter plot command to obtain plots showing how the

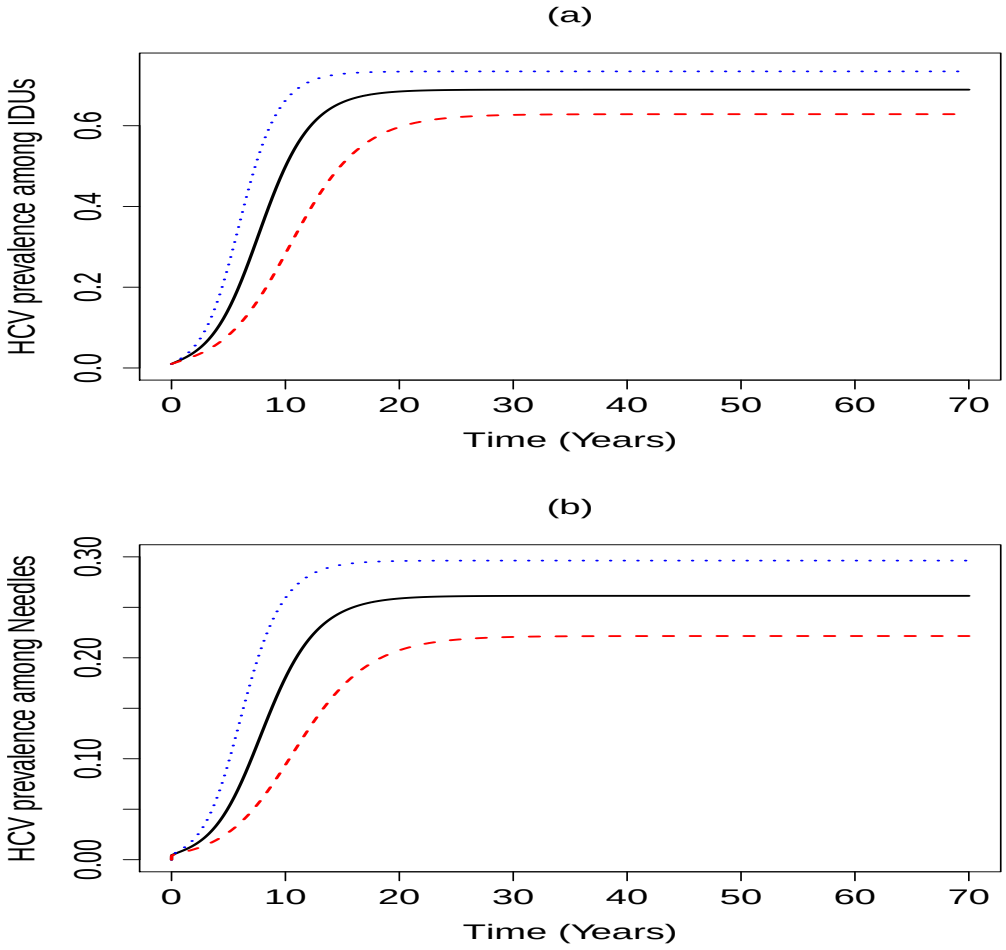

Figure 4.6: HCV prevalence prevalence among (a) sharing IDUs and (b) needles with $\lambda = 92.7$ (red dashed line), 103 (solid black line) and 113.3 (dotted blue line). Initially $\pi_x(0) = 0.99$, $\pi_{h_1}(0) = 0.01$ and $\pi_{x_1}(0) = \pi_{h_2}(0) = \pi_y(0) = \pi_z(0) = \beta_{h_1}(0) = \beta_{h_2}(0) = \beta_y(0) = 0$.

endemic equilibrium prevalence of HCV among both IDUs and needles behaves over a range of needle and syringe sharing estimates (Figure 4.7). These simulations show that changing the value of λ will result in similar model behaviour for both IDUs and needles.

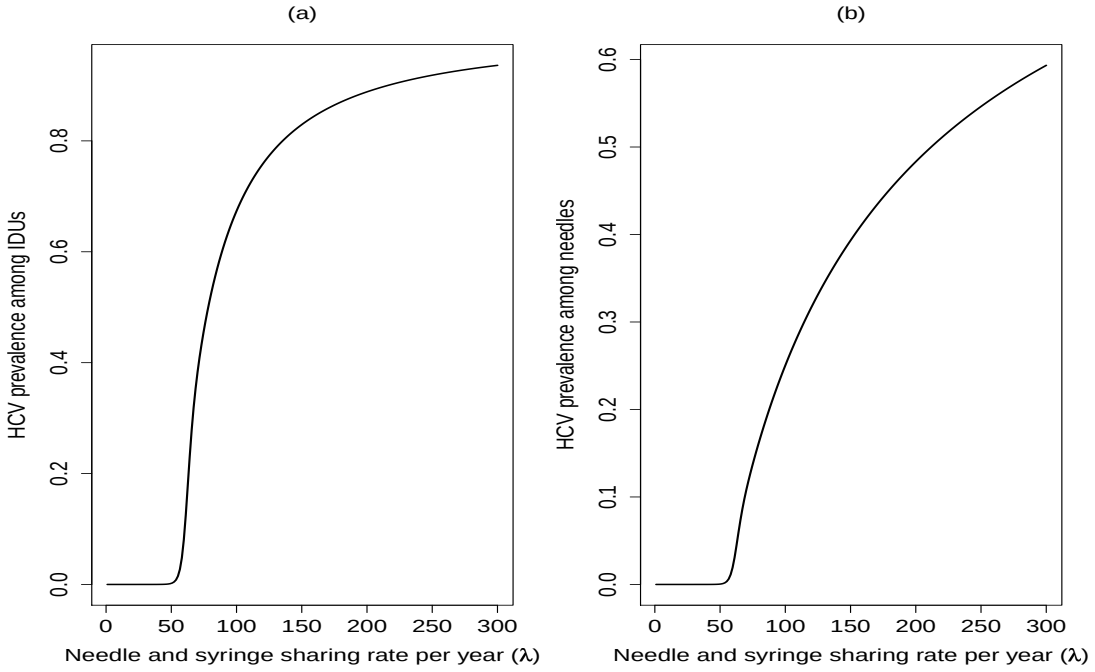

Figure 4.7: Parameter plot of needle and syringe sharing rate (λ) vs HCV prevalence among (a) sharing IDUs and (b) needles.

4.9.2 Changes in model behaviour resulting from different needle cleaning probabilities

As with needle and syringe sharing rates, the data used to estimate the needle cleaning probability ϕ comes from self assessment questionnaires, which raises questions about the reliability of the data and the effectiveness of the cleaning procedure in removing HCV viral load. In this subsection we examine the different model behaviours which result from different estimates for the probability of successful needle cleaning. First of all we obtain parameter plots to show how the endemic HCV prevalence for both sharing IDUs and needles changes over a range of ϕ estimates (see Figure 4.8). Although these simulations show the relationship between the endemic HCV prevalence and the value of ϕ for both sharing IDUs and needles, we are interested in how our long term prevalence estimate changes when we have different needle cleaning probabilities. Successful needle and syringe cleaning is just one way to control the spread of HCV and in the following simulations we examine what effect a 10%, 20% and 50% increase

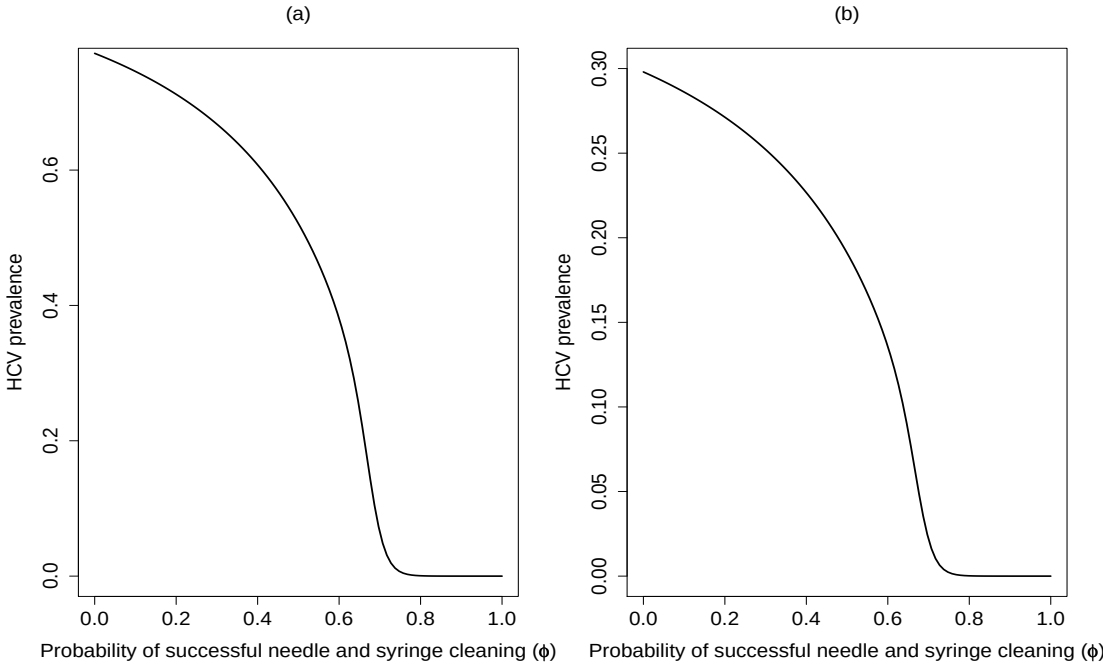

Figure 4.8: Parameter plot of probability of successful needle and syringe cleaning (ϕ) vs HCV prevalence among (a) IDUs and (b) needles.

in successful needle cleaning has on our model predictions of HCV prevalence for both sharing IDUs and needles.

Figure 4.9 and Table 4.6 show how the model behaviour and endemic equilibrium values both IDUs and needles change when the different needle cleaning probability estimates are applied. Increasing the value of ϕ reduces the resulting value of R_0 which results in a slower disease spread and smaller endemic equilibrium value. Furthermore, we can see from Table 4.6 that an increase of 10%, 20% or 50% in ϕ will reduce long term HCV prevalence estimates for sharing IDUs by 1.1%, 2.4%, and 6.9% respectively. Our model simulations also suggest that increasing ϕ in this way will result in the proportion of infectious needles in circulation decreasing by 0.5%, 1%, and 2.9% respectively.

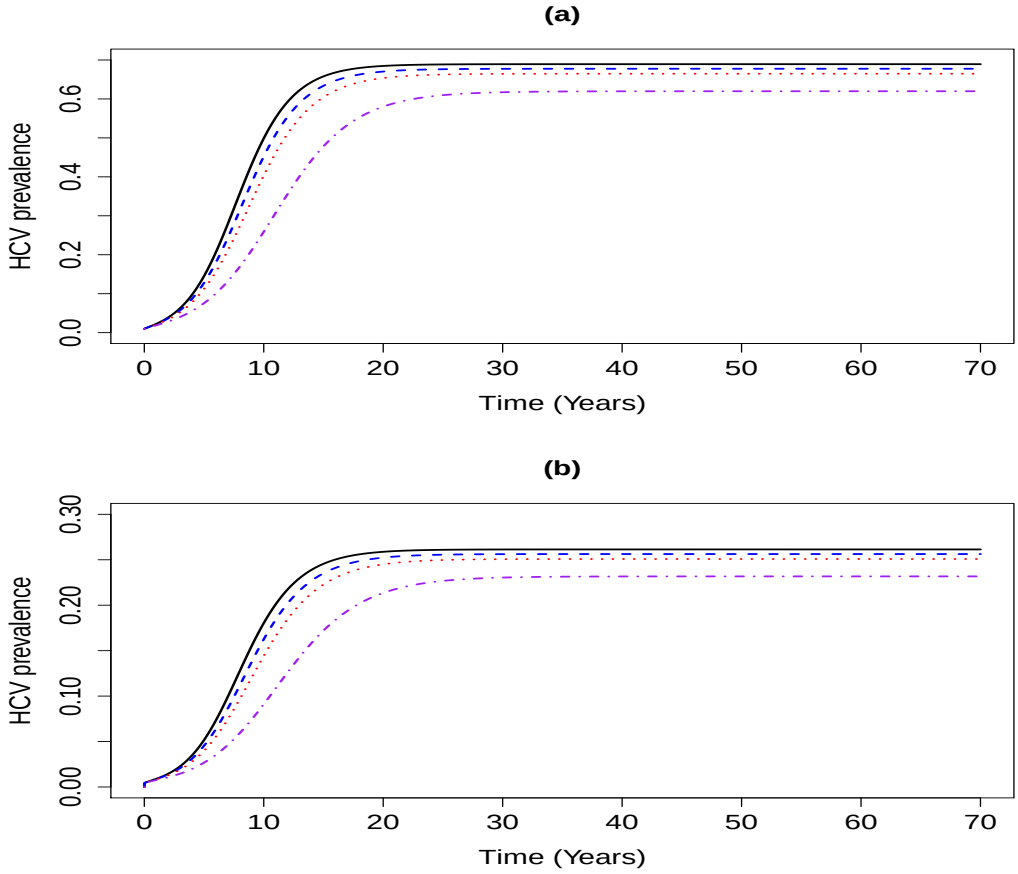

Figure 4.9: HCV prevalence estimates for (a) sharing IDUs and (b) needles with probability of successful needle and syringe cleaning $\phi = 0.255$ (solid black line), 0.2805 (dashed blue line), 0.306 (red dotted line) and 0.3825 (purple dotdash line). Initially $\pi_x(0) = 0.99$, $\pi_{h_1}(0) = 0.01$ and $\pi_{x_1}(0) = \pi_{h_2}(0) = \pi_y(0) = \pi_z(0) = \beta_{h_1}(0) = \beta_{h_2}(0) = \beta_y(0) = 0$.

ϕ	Sharing IDU HCV prevalence	Needle HCV prevalence
0.255	0.689	0.261
0.2805	0.678	0.256
0.306	0.665	0.251
0.3825	0.620	0.232

Table 4.6: Endemic equilibrium HCV prevalence estimates for both sharing IDUs and needles for different ϕ estimates.

4.9.3 Evaluating the impact of different needle turnover rates

In our earlier simulations we found that to eliminate HCV in our population we required a dramatic increase in the needle turnover rate (τ). In these simulations we examine the effect of a 10%, 20% or 50% increase in our estimate of the needle turnover rate on long term HCV prevalence estimates for both IDUs and needles. As in our earlier simulations, we obtain graphs showing how the model behaviour and endemic equilibrium values differ under each condition and summarise the final endemic values in a table (see Figure 4.10 and Table 4.7). Figure 4.10 shows that an increase in the needle turnover rate will result in a slower disease spread in the population and a lower endemic equilibrium value. This makes sense since an increase in needle turnover will result in a reduction in the basic reproductive number R_0 and hence reduce the level of HCV in the population. Furthermore, we can see from Table 4.7 that increasing the needle turnover rate by 10%, 20% or 50% will reduce long term HCV prevalence estimates for IDUs by 1.8%, 3.7%, and 9.5% respectively. These increases will also affect the total proportion of

τ (per year)	Sharing IDU HCV prevalence	Needle HCV prevalence
133	0.689	0.261
146.3	0.671	0.240
159.6	0.652	0.220
199.5	0.594	0.172

Table 4.7: Endemic equilibrium values for different needle turnover rates.

infectious needles in circulation. Again from Table 4.7, we can see that increasing our needle turnover rate in this way will result in an estimated 2.1%, 4.1%, and 8.9% reduction in the proportion of infectious needles in circulation.

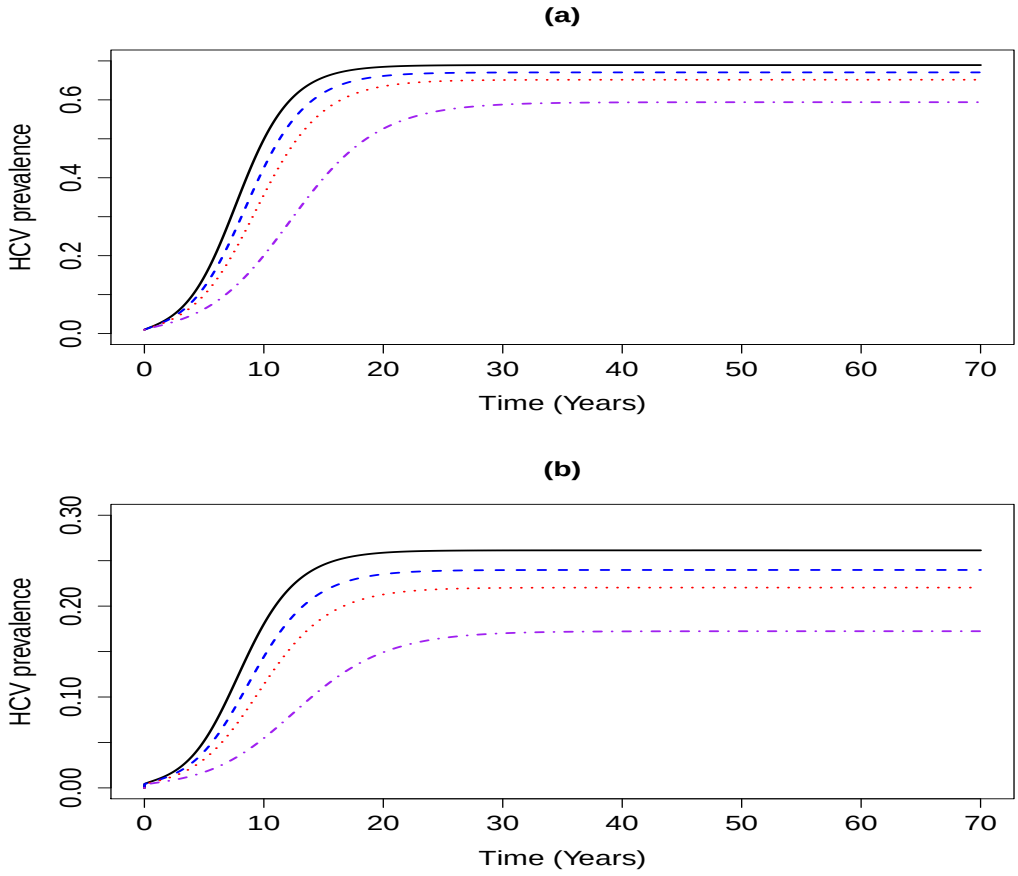

Figure 4.10: HCV prevalence estimates for (a) IDUs and (b) needles with a needle turnover rate $\tau = 133$ per year (solid black line), 146.3 per year (dashed blue line), 159.6 (dotted red line) and 199.5 per year (purple dotdash line).

In order to clarify what is meant by a 10%, 20% or 50% increase in needle turnover rate we calculate the number of needles that health organisations would need to distribute to all IDUs in order to achieve this target. Performing a similar calculation to the one performed in Subsection 4.5.3, we first calculate the working life of a needle under each assumed turnover rate. Using these values and the assumption that IDUs inject at the rate of 1.62 times per day, we calculate, for each working life, the number of times the needle is used before it is changed. Taking these values and again assuming that there are 4,679,538 injections taking place each year, we can calculate the number of needles that health organisations would need to distribute to IDUs (Table 4.8).

These results suggest that increasing the number of needles distributed to all

τ (per year)	Number of needles needed to meet target
133	1,049,770
146.3	1,157,024
159.6	1,262,207
199.5	1,577,759

Table 4.8: The number of needles health organisations would need to distribute to meet different needle turnover rates.

IDUs from 1,049,770 to 1,157,024 will reduce long term HCV prevalence estimates by 1.8% and will result in 2.1% fewer infectious needles in circulation. These results are presented in Table 4.9.

Increase in needles distributed	Decrease in HCV prevalence	Decrease in infectious needles
107,254	1.8%	2.1%
212,437	3.7%	4.1%
527,989	9.5%	8.9%

Table 4.9: Effect of distributing more needles on HCV prevalence and the number of infectious needles in circulation.

4.9.4 The influence of the probability of HCV transmission for chronic infection on model predictions

We have seen from our literature search that some HCV models assume that the probability of chronic HCV transmission is the same as the probability of acute HCV transmission. On the other hand other models, including ours, assume that there is a difference between the two. In Vickerman *et al.* (2009) good model fits were obtained when using different transmission probabilities as well as when transmission probabilities are assumed to be the same.

In this subsection we will investigate how these two different assumptions affect our estimates of long term HCV prevalence. Our first set of simulations involve parameter plots of how endemic equilibrium prevalence for both IDUs and needles change as the chronic transmission probability α_y takes different values. Figure 4.11 shows the results of these simulations with Figure 4.11 (a) showing the general relationship between HCV prevalence among sharing IDUs and α_y and Figure 4.11 (b) showing the relationship of this parameter with the equilibrium HCV prevalence in needles.

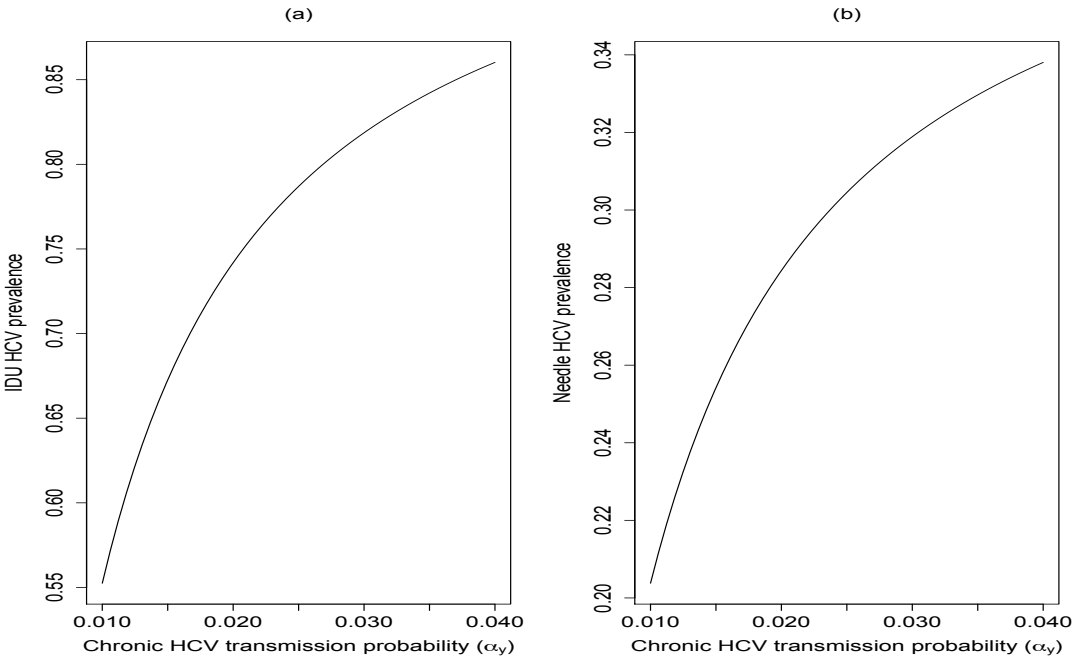

Figure 4.11: Parameter plots of chronic HCV transmission probability α_y vs long term HCV prevalence in (a) sharing IDUs and (b) needles.

These figures show that increasing or decreasing α_y will result in similar model behaviour for both IDUs and needles. To investigate how our model predictions change with different values of α_y we ran three simulations altering α_y only. Our first simulation assumed different transmission probabilities for acute and chronic HCV infection according to our baseline parameter estimates of $\alpha_h = 0.0432$ and $\alpha_y = 0.016$. The second simulation assumes that acute and chronic HCV infection have the same transmission probability with $\alpha_h = \alpha_y = 0.0432$. The third simulation assumes $\alpha_h = 0.0432$ and $\alpha_y = 0.0296$, the latter was chosen because it is halfway between our baseline estimate and the second simulation estimate of $\alpha_y = 0.0432$. The results of these simulations are shown in Figure 4.12. Figure 4.12 (a) shows how the proportion of infectious IDUs behaves when the different chronic transmission probabilities are applied. Furthermore, we can see that this behaviour is similar to that in Figure 4.12 (b) which shows the behaviour of infectious needles under the same conditions, exactly as suggested by Figure 4.11. In order to see the effects these changes in α_y have more clearly, we have again summarised the equilibrium values under each condition in a table

(see Table 4.10).

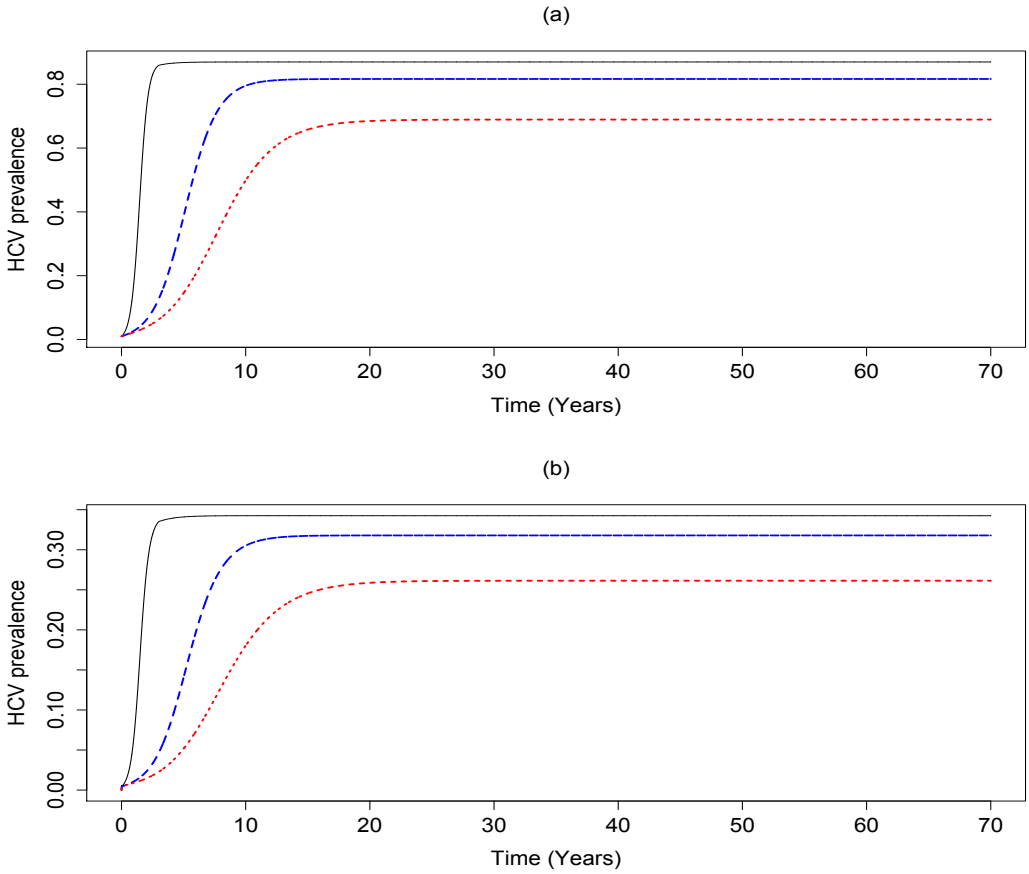

Figure 4.12: HCV prevalence estimates for (a) sharing IDUs and (b) needles when $(\alpha_h, \alpha_y) = (4.32\%, 1.6\%)$ (dotted red line), (4.32%, 2.96%) (blue dashed line) and (4.32%, 4.32%) (solid black line).

We can see from Figure 4.12 that increasing the transmission probability of chronic HCV results in a more aggressive disease spread through our population. This can be seen by the steeper gradients of the blue dashed and solid black lines along with the shorter time to endemic equilibrium. The endemic equilibrium values for the higher transmission probabilities are greater than our baseline parameter estimate of $\alpha_y = 0.016$. In fact, increasing α_y in our model so that $\alpha_y = \alpha_h$ would result in an HCV prevalence increase of 18.1% which suggests that this parameter, though difficult to estimate, must be estimated as accurately as possible otherwise prevalence estimates and the levels of intervention needed for disease elimination could be easily under-estimated.

α_y	Sharing IDU HCV prevalence	Needle HCV prevalence
0.0160	0.689	0.261
0.0296	0.817	0.318
0.0432	0.870	0.343

Table 4.10: Long term HCV prevalence estimates for both sharing IDUs and needles with different chronic transmission probabilities.

4.9.5 The influence of the probability of HCV transmission for acute infection on model predictions

While searching the literature for parameter estimates we identified a range of estimates for the probability of acute HCV transmission (see Table 4.2). In the following simulations we examine how the different estimates for this parameter affect the long term estimates of our transmission model. As with other simulations we obtain parameter plots to show how the proportion of antibody positive IDUs change over a range of α_h estimates (see Figure 4.13).

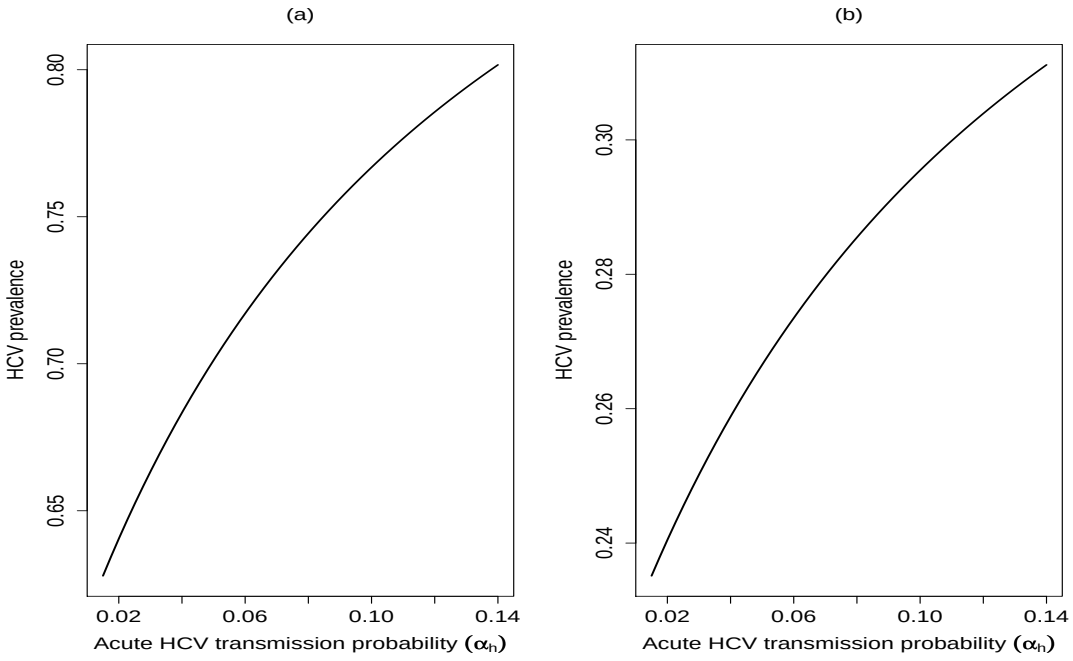

Figure 4.13: Parameter plots of chronic HCV transmission probability α_h vs long term HCV prevalence in (a) sharing IDUs and (b) needles.

We have seen from Table 4.2 that estimates for this parameter generally range

from 1.3% to 5%, with an upper bound of 14% suggested by Vickerman *et al.* (2009). We exclude the 20-30% estimate in Hutchinson *et al.* (2006) since we do not model this period of 6-8 weeks explicitly. In our next set of simulations we will examine the long term prevalence when $\alpha_h = 0.016, 0.026, 0.0432$, 0.05 and 0.14. Figure 4.14 shows how the model behaviour changes with each parameter estimate. As expected, a lower estimate for α_h reduces the final equilibrium value and the speed at which the disease spreads through our population. Similarly, a higher estimate for this parameter results in faster disease spread and a greater endemic equilibrium value.

To see how these final estimates for HCV prevalence change under each assumption we have summarised the equilibrium values in a table (see Table 4.11). From this table we can see that increasing our estimate of α_h from 0.016 to 0.05 results in the long term prevalence estimate increasing by 7.1%. Since small increases in α_h result in larger changes in HCV prevalence, it suggests that accurate predictions will rely on an accurate estimate for this parameter.

α_h	HCV prevalence among sharing IDUs
0.016	0.630
0.026	0.655
0.0432	0.689
0.05	0.701
0.14	0.802

Table 4.11: Model predictions for different acute transmission probabilities.

4.9.6 How the proportion of IDUs that can spontaneously resolve HCV infection affects model predictions

During our literature search for parameter estimates we noted that estimating the proportion of IDUs that spontaneously resolve HCV infection is extremely difficult since the majority of cases are asymptomatic and therefore go undiagnosed. The results of the systematic review into spontaneous viral clearance (Micallef *et al.* 2006) suggest that the rate of spontaneous viral clearance is 26%. However, other authors have suggested a range of values with Hutchinson *et al.* (2006) assuming 15-40%, Vickerman *et al.* (2007) assuming 18-50%, and Kamal (2008) suggesting 10-60% before stating that the general rule of thumb is 20-40%.

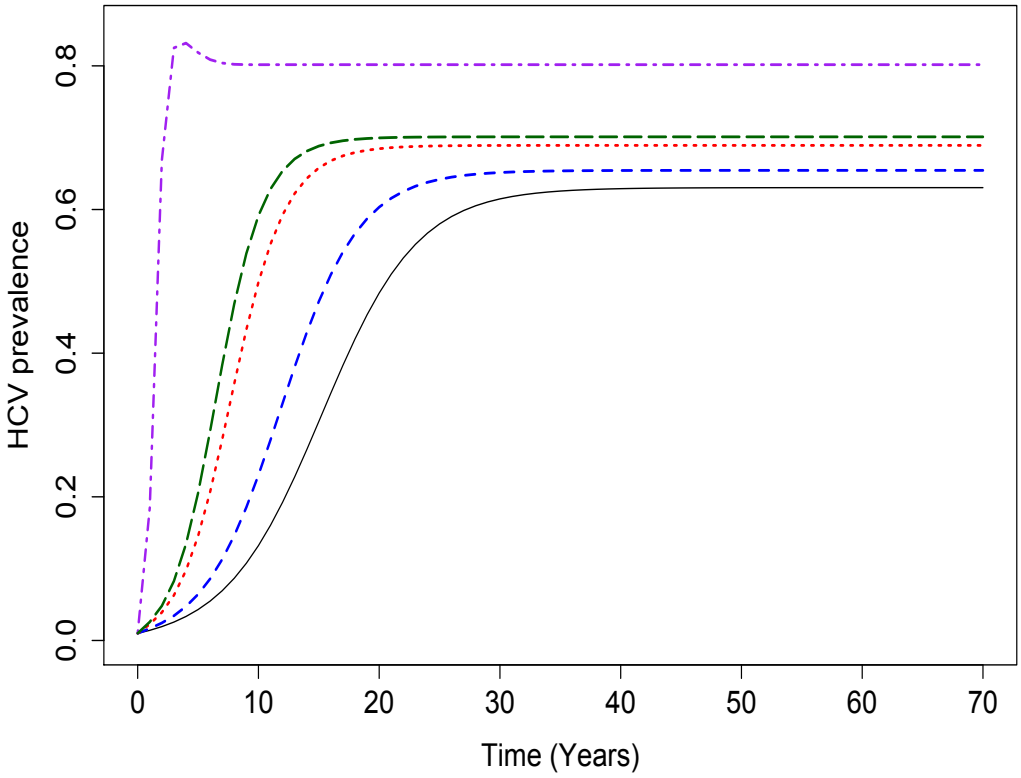

Figure 4.14: HCV prevalence estimates when acute HCV transmission probability $\alpha_h = 0.016$ (solid black line), 0.026 (blue dashed line), 0.0432 (red dotted line), 0.05 (dark green long dash line) and 0.14 (purple dotdash line). In all simulations $\alpha_y = 0.016$.

In this subsection we are going to examine how these differing assumptions affect our equilibrium estimates of HCV prevalence and the proportion of infectious IDUs in the population.

Our current estimate for the spontaneous viral clearance parameter is $\delta = 0.26$, in accordance with the Micallef *et al.* systematic review and Vickerman *et al.* (2009). Given that this estimate is in the middle of the ranges suggested by the other authors, it makes sense to see what happens either side of our current estimate. We therefore conduct simulations assuming that 15%, 26% or 50% of IDUs can spontaneously resolve their infection, corresponding to the lowest estimate suggested by Hutchinson *et al.* (2006), our current estimate for

this parameter, and the highest estimate suggested by Vickerman *et al.* (2007). Figure 4.15 and Table 4.12 show the results of these simulations.

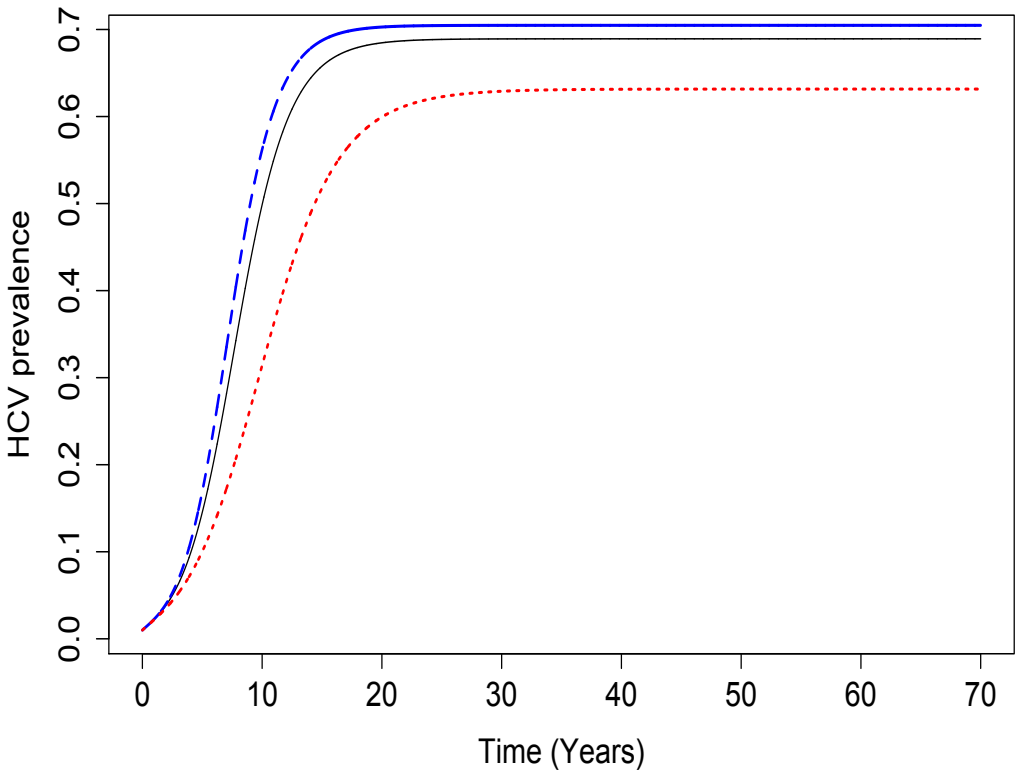

Figure 4.15: Equilibrium HCV prevalence estimates when the proportion of IDUs that spontaneously resolve HCV infection $\delta = 0.15$, 0.26 and 0.5.

δ	HCV prevalence
0.15	0.705
0.26	0.689
0.5	0.632

Table 4.12: Endemic equilibrium values for both antibody positive and infectious IDUs when $\delta = 0.15$, 0.26, 0.5.

The results of these simulations show that increasing the value of δ results in a lower endemic equilibrium value and a slower disease spread. Altering the value for δ by a relatively small amount will result in very similar model predictions.

Our simulations show that decreasing our estimate to $\delta = 0.15$ results in our long term HCV prevalence estimates increasing by only 1.6%. In a similar way, we can see that increasing δ from 0.26 to 0.5 reduces our long term prevalence estimates by 5.7%. Either way, it is clear that there is not much change in our model behaviour when this parameter is varied.

4.9.7 The effect of immunity on model estimates

We know from our literature search and systematic review (Corson *et al.* 2011), see also Chapter 2, that there is much uncertainty surrounding the existence of an immune state as well as the rate of progression to this state. Published articles in this area are often contradictory: different authors report evidence of no immunity, partial immunity and even total immunity to HCV re-infection. How this level of uncertainty affects model estimates of HCV prevalence is an important question for modellers, and one which we investigate in the following simulations.

Of those IDUs who spontaneously resolve their HCV infection, our model assumes that a proportion α become immune to HCV re-infection. In each simulation we assume a different value for α, and by keeping all other parameters constant, estimate HCV prevalence among Glasgow IDUs. We run several simulations assuming that either 0%, 12.5%, 25%, 50%, or 100% of the spontaneous resolvers become immune. Figure 4.16 shows the graphical results of these simulations.

Proportion that become immune (α)	HCV prevalence estimate
0%	0.705
12.5%	0.697
25%	0.689
50%	0.675
100%	0.645

Table 4.13: Model predictions for different immunity assumptions.

From Figure 4.16 we can see that assuming anywhere between 0 and 50% immunity does not dramatically change our model predictions. To further see the effects that different immunity assumptions have on our estimates we have summarised the results in Table 4.13. This table shows how the endemic es-

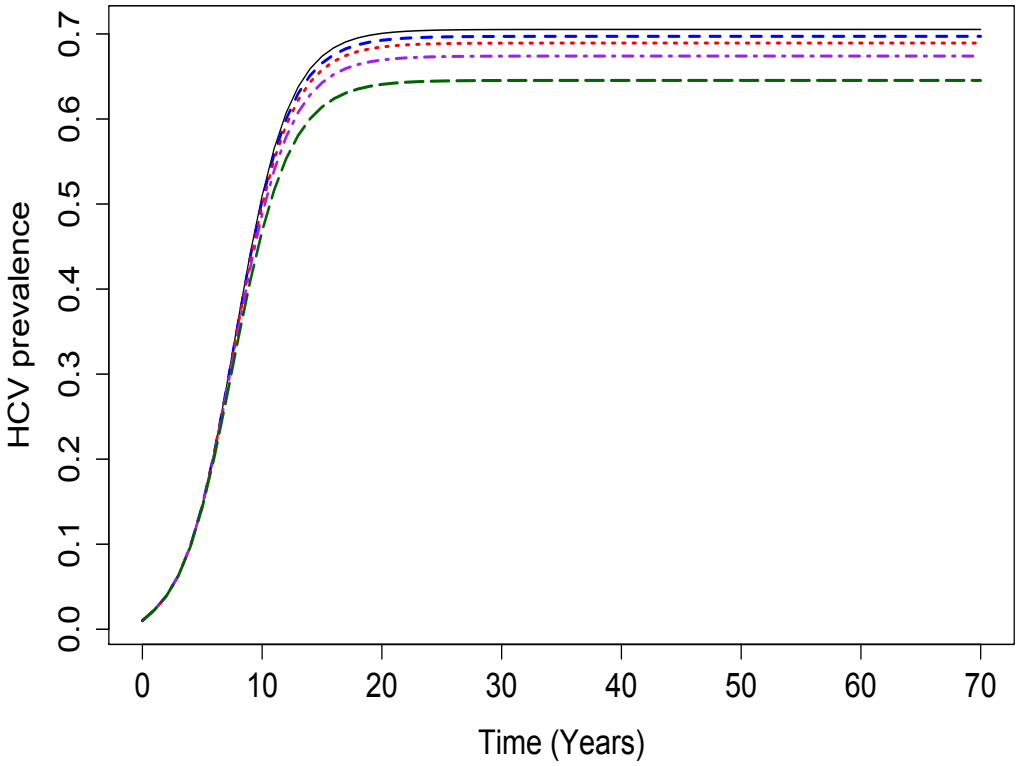

Figure 4.16: Simulations of endemic equilibrium HCV prevalence estimates when the proportion of IDUs that become immune to HCV re-infection $\alpha = 0$ (solid black line), 0.125 (dashed blue line), 0.25 (dotted red line), 0.5 (purple dotdash line) and 1 (dark green long dash line).

timate of HCV prevalence among Glasgow IDUs changes for different levels of immunity. Recent publications have documented HCV re-infection in humans so it is reasonable to assume that 100% immunity is unrealistic. Table 4.13 shows that prevalence estimates made while assuming no protective immunity are only 6% greater than those estimates made assuming total immunity to re-infection. Therefore, the uncertainty surrounding immunity to HCV re-infection does not invalidate our model predictions. Given this lack of variation in prevalence estimates we can speculate that the inclusion of an immune class is not wholly necessary to obtain accurate model predictions.

4.10 Conclusions and discussion

In this chapter numerical simulations have verified that the model tends to an endemic equilibrium value with realistic parameter values giving a HCV prevalence estimate of 69%, compared to the current estimated prevalence of 70% among Glasgow IDUs (NESI 2010) and 80% among needle and syringe sharing IDUs. Thus, the observed prevalence of HCV among needle and syringe sharing IDUs is greater than our model estimate (80% versus 69% respectively) and there could be a number of reasons for this under-estimation. For example, our IDU and needle interaction assumptions were optimistic (i.e. needles are left in the infectious state of the last user) which gives a lower bound on HCV prevalence among needle and syringe sharing IDUs. Other assumptions on key parameters such as (i) the homogeneity in sharing rates by time since onset of injecting among IDUs and (ii) conservative estimates of the probability of HCV transmission, may also contribute to our under-estimation.

The results of these simulations confirmed our analytical results and allowed us to use the model to estimate the level of intervention required to give $R_0 \leq 1$ and therefore eliminate HCV in all IDUs and needles. Analytical techniques have enabled us to derive expressions for the critical values of needle and syringe sharing rates (λ), needle cleaning (ϕ) and needle turnover (τ) that are needed to achieve $R_0 = 1$. Our analysis, which was confirmed by simulations, shows that provided that all other parameters remain fixed each of $\lambda \leq 54.67$ per year, $\phi \geq 0.74$ and $\tau \geq 562.37$ per year results in $R_0 \leq 1$ and eventual HCV elimination in IDUs and needles. Further simulations have showed that increasing the level of intervention beyond these critical values results in a faster time to disease free equilibrium. Our critical sharing rate of $\lambda \leq 54.67$ shows that we would need a minimum 47% reduction in needle and syringe sharing rates before notable decreases in HCV prevalence are observed. This is comparable to findings reported by both Murray *et al.* (2003) and Vickerman *et al.* (2007), in that sharing rates (defined as number of sharing partners per year by Murray *et al.* and the number of receptive syringe shares per month by Vickerman *et al.*) would need to decrease by 50% and 25-50%, respectively, for HCV seroprevalence to fall.

While these results showed that targeted interventions can result in HCV elimination, they also showed that the level of intervention required over a pro-

longed period may be unreasonable to sustain. Since it is unreasonable to assume that our behavioural parameter estimates will hold for such a long period of time, further work showed that intervention measures that target more than one risk area are the most effective way to achieve this. This would allow health organisations to devote more resources to risk behaviours which will result in the largest differences, such as needle cleaning and sharing, while maintaining a constant level in more difficult interventions such as needle turnover.

Using Berkeley Madonna we further varied all three control parameters (λ, ϕ and τ) simultaneously to find the combination which gives $R_0 = 1$. Our results suggest that to achieve $R_0 = 1$ we require the needle and syringe sharing rate (λ) to reduce from 103 to 73.6 per year, the needle turnover rate (τ) to increase from 134 to 253 per year and the level of successful needle and syringe cleaning (ϕ) would need to increase from 0.255 to 0.283. It is not unrealistic to expect that changes or improvements in one control parameter will likely relate or influence changes in another parameter. For example, increases in needle and syringe sharing provision will lead to increases in the needle turnover rate which in turn would likely have a positive effect by also reducing the needle and syringe sharing rate. A greater understanding is therefore needed, through the further analysis of observational data, on the relationship between these control parameters and the extent to which one is associated with another (Hutchinson, Bird *et al.* 2006).

Parameterising a disease transmission model is extremely difficult, especially when there are no clear parameter values in the literature. We have seen that small variations in some parameters, such as transmission probabilities can have a relatively large effect on model predictions, while others do not have such an effect, such as the proportion that become immune. Since transmission models are used to evaluate the effectiveness of intervention measures and explore the possibility of disease elimination, this kind of analysis is crucial in identifying the parameters that need to be estimated as accurately as possible.

The model assumes that IDUs who share select needles and syringes at random from those available. However, in practice this will not be the case. Some IDUs are very careful about keeping their own syringes and are more likely to share in small groups or with sexual partners. This is a limitation of the model. In effect there will be two groups, one group who share needles and syringes infrequently and another who share frequently. Applying an average sharing rate over the

whole population could result in our model over-estimating HCV transmission among IDUs as in the HIV model of Greenhalgh (1997). Furthermore, we have assumed that infectious needles and syringes do not lose their infectivity if they are left unused for a period of time. This assumption serves to increase the number of infectious needles in circulation. Therefore, it is important to know the survival time of HCV in needles and syringes. Since survey data suggests the working life of a needle is approximately 2.75 days and HCV can remain viable in syringes for up to 63 days (Paintsil *et al.* 2010) we do not feel that this assumption would have a great impact on our results.

In summary, we have developed and analysed a mathematical model that approximates the spread of HCV among IDUs, and despite a number of simplifying assumptions we have obtained reasonable prevalence predictions. Furthermore, we have shown that targeted interventions can reduce HCV prevalence amongst the Glasgow IDU population. Our next step is to develop a more realistic transmission model by making fewer simplifying assumptions.

Chapter 5

Modelling the highly infectious acute stage of infection

Initial HCV infection may be followed by a short six to eight week period of high viraemia (Simmonds *et al.* 1998); a phenomenon similar to HIV. Estimates for the infectivity of HIV at different stages of infection suggest that there is a ten-fold increase in infectivity during this high phase of viraemia (Longini *et al.* 1989; Vickerman and Watts 2005). As information on the infectivity of HCV during this high viraemic period does not exist a similar behaviour to HIV is sometimes assumed.

However, HCV transmission models such as those by Vickerman *et al.* (2007, 2009) as well as our initial model developed in Chapter 3 do not explicitly model the highly infectious acute phase of infection. Instead they model a single acute stage with a single transmission probability. It can be assumed that this single transmission probability is simply an average of both the high and low transmission probabilities taken over the total length of the acute phase.

In this chapter we extend the HCV transmission model developed in Chapter 3 to explicitly model the proportion of IDUs in the highly infectious acute stage of infection. We first describe the model and its assumptions that allow IDUs in the population to progress through the different stages of infection. Then using these assumptions we derive the governing system of differential equations. Next we derive an expression for the basic reproductive number R_0 before analysing the behaviour of the model numerically using the software package Berkeley Madonna version 8.3.11 (Macey *et al.* 2000).

5.1 IDU population

We have taken the model structure used in Chapter 3 (Figure 3.1) and separated the acute h_1 and h_2 stages into two, one for the period of high viraemia (denoted $h_1^\dagger$ and $h_2^\dagger$) and one for the period with low viraemia (denoted h_1 and h_2). This is illustrated in Figure 5.1. The assumptions used in Chapter 3 still hold.

The force of infection experienced by a single susceptible IDU is given by $f = \lambda(1-\phi)(\alpha_h^\dagger\beta_h^\dagger + \alpha_h\beta_h + \alpha_y\beta_y)$. Here λ is the average rate that IDUs share needles and syringes; ϕ is the probability that an IDU will successfully clean their needle and syringe prior to use (successful cleaning requires IDUs to clean their injecting equipment with alcohol or bleach so that there is no HCV viral load present); $\alpha_h^\dagger$, α_h and α_y are the transmission probabilities relating to acute and chronic HCV infection, respectively, via shared needles and syringes ($\alpha_h^\dagger$ represents the infectivity of HCV during the highly infectious acute stage); and $\beta_h^\dagger$, β_h and β_y are respectively the fractions of highly infectious acutely infected, acutely infected and chronically infected needles and syringes. $\beta_h^\dagger = \beta_{h_1}^\dagger + \beta_{h_2}^\dagger$, the sum of the fractions of the two types ($\beta_{h_1}^\dagger$ and $\beta_{h_2}^\dagger$) of highly infectious acutely infected needle and syringes. Similarly $\beta_h = \beta_{h_1} + \beta_{h_2}$.

Susceptible IDUs, once infected with HCV, will progress to the highly infectious acute stage of infection (either $h_1^\dagger$ or $h_2^\dagger$). A proportion δ of these newly infected IDUs will progress to the acute $h_2^\dagger$ class. After a period of time these IDUs will progress to the acute h_2 class, where they are less infectious. At the end of their time in this class these IDUs clear the virus spontaneously with a proportion α becoming immune to HCV re-infection and the remaining $(1-\alpha)$ becoming susceptible to HCV re-infection (Farci *et al.* 1992; Mehta *et al.* 2002; Micallef *et al.* 2007). The remaining proportion $(1-\delta)$ of newly infected IDUs progress to the acute $h_1^\dagger$ class: these IDUs will progress to the acute h_1 class before they progress to chronic infection where they will remain until they either die or leave the sharing injecting population.

IDUs progress from the highly infectious acute stage of infection (either $h_1^\dagger$ or $h_2^\dagger$) to the acute stage of infection (h_1 or h_2) at per capita rate σ_1, so that conditional on not leaving the sharing, injecting population, the average time that an IDU spends in the highly infectious acute stage of infection is $1/\sigma_1$ time units. Similarly, IDUs leave the acute stage of infection (h_1 or h_2) at per capita

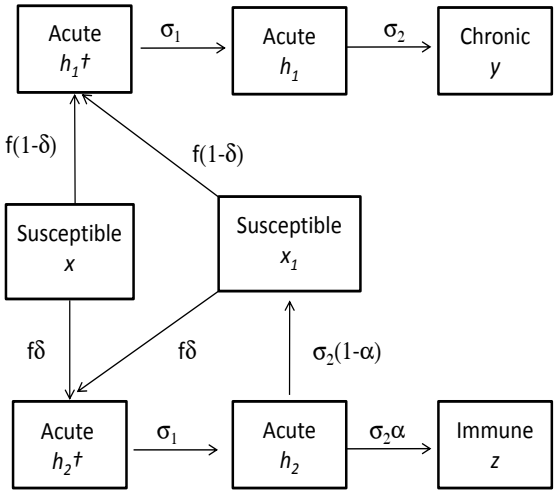

Figure 5.1: HCV transmission flow diagram. The arrows in the diagram indicate the possible transitions for IDUs between stages of HCV infection and the parameters shown are the per capita rate of flow between the stages. The rate of recruitment to the population and the rate at which IDUs leave the population (μ) are not shown.

rate σ_2.

5.2 Needles and syringes

As in our simple model, we also model the number of needles and syringes (m) by HCV infection status (i.e. either uninfected, acutely infected or chronically infected) over time. IDUs can become infected only through the sharing of needles and syringes used by a HCV acutely or chronically infected IDU. Thus the infectivity of each needle is determined by the infectivity of the IDU who last used the needle, with needles that have never been used being uninfectious.

5.3 Governing equations

Let $\pi_x(t)$, $\pi_{x_1}(t)$, $\pi^\dagger_{h_1}(t)$, $\pi_{h_1}(t)$, $\pi^\dagger_{h_2}(t)$, $\pi_{h_2}(t)$, $\pi_y(t)$, $\pi_z(t)$ denote respectively the fraction of IDUs in the x-susceptible, x_1-susceptible, highly infectious acute $h^\dagger_1$, acute h_1, highly infectious acute $h^\dagger_2$, acute h_2, chronic y and immune z classes at time t. In a similar way $\beta^\dagger_h(t)$, $\beta_h(t)$ and $\beta_y(t)$ denote respectively the fraction of needles in the highly infectious acute, acute and chronic stages of HCV infection at time t. We define the constant IDU to needle ratio $\gamma = n/m$ to be the number of IDUs per needle in the population. Then, using a similar method to that already used in Chapter 3, our governing equations are given by

$$\frac{d\pi_x}{dt} = \mu - \mu\pi_x - \lambda\pi_x(1-\phi)(\alpha^\dagger_h\beta^\dagger_h + \alpha_h\beta_h + \alpha_y\beta_y), \tag{5.1}$$

$$\frac{d\pi_{x_1}}{dt} = \sigma_2(1-\alpha)\pi_{h_2} - \mu\pi_{x_1} - \lambda\pi_{x_1}(1-\phi)(\alpha^\dagger_h\beta^\dagger_h + \alpha_h\beta_h + \alpha_y\beta_y), \tag{5.2}$$

$$\begin{aligned}\frac{d\pi^\dagger_{h_1}}{dt} =& \lambda(1-\phi)(1-\delta)(1-\pi^\dagger_{h_1} - \pi_{h_1} - \pi^\dagger_{h_2} - \pi_{h_2} - \pi_y - \pi_z) \\ & (\alpha^\dagger_h\beta^\dagger_h + \alpha_h\beta_h + \alpha_y\beta_y) - (\mu+\sigma_1)\pi^\dagger_{h_1},\end{aligned} \tag{5.3}$$

$$\begin{aligned}\frac{d\pi^\dagger_{h_2}}{dt} =& \lambda(1-\phi)\delta(1-\pi^\dagger_{h_1} - \pi_{h_1} - \pi^\dagger_{h_2} - \pi_{h_2} - \pi_y - \pi_z) \\ & (\alpha^\dagger_h\beta^\dagger_h + \alpha_h\beta_h + \alpha_y\beta_y) - (\mu+\sigma_1)\pi^\dagger_{h_2},\end{aligned} \tag{5.4}$$

$$\frac{d\pi_{h_1}}{dt} = \pi^\dagger_{h_1}\sigma_1 - (\mu+\sigma_2)\pi_{h_1}, \tag{5.5}$$

$$\frac{d\pi_{h_2}}{dt} = \pi^\dagger_{h_2}\sigma_1 - (\mu+\sigma_2)\pi_{h_2}, \tag{5.6}$$

$$\frac{d\pi_y}{dt} = \sigma_2\pi_{h_1} - \mu\pi_y, \tag{5.7}$$

$$\frac{d\pi_z}{dt} = \sigma_2\alpha\pi_{h_2} - \mu\pi_z, \tag{5.8}$$

$$\frac{d\beta^\dagger_h}{dt} = \lambda\gamma(\pi^\dagger_{h_1} + \pi^\dagger_{h_2} - \beta^\dagger_h) - \tau\beta^\dagger_h, \tag{5.9}$$

$$\frac{d\beta_h}{dt} = \lambda\gamma(\pi_{h_1} + \pi_{h_2} - \beta_h) - \tau\beta_h, \tag{5.10}$$

$$\frac{d\beta_y}{dt} = \lambda\gamma(\pi_y - \beta_y) - \tau\beta_y, \tag{5.11}$$

with suitable initial conditions: $\pi_i(0) \geq 0$ and $\sum_i \pi_i = 1$ where $i = x, x_1, h_1^\dagger, h_1, h_2^\dagger, h_2, y, z$. $\beta_j(0) \geq 0$ and $\sum_j \beta_j \leq 1$ where $j = h^\dagger, h, y$.

Equations (5.1)-(5.8) describe how the proportion of IDUs at each stage of HCV infection changes over time while equations (5.9)-(5.11) describe how the proportion of infectious needles changes over time in our model.

5.4 The basic reproductive number R_0

To derive the basic reproductive number for this extended model we again consider a newly infected IDU entering a disease free population containing only susceptible IDUs. As before, the infection process can be broken into two stages:

1. The IDU passes the infection to uninfected needles.

2. The newly infected needles then infect susceptible IDUs.

Using a similar method to that used in Section 3.3, we first derive the expected number of infectious needles generated from a single infectious IDU during their lifetime. We then derive the expected number of infected IDUs resulting from these infectious needles. A single IDU shares needles and syringes at a rate λ and once infected with HCV moves into the acute $h_1^\dagger$ class with probability $(1-\delta)$ where they remain for an average $1/(\mu+\sigma_1)$ time units. They then progress to the acute h_1 stage with probability $\sigma_1/(\mu+\sigma_1)$ where they remain for $1/(\mu+\sigma_2)$ time units. They then move to the chronic stage of infection with probability $\sigma_2/(\mu+\sigma_2)$ where they remain for an average $1/\mu$ time units, otherwise they leave the population. This IDU, once infected, can also move into the acute $h_2^\dagger$ class with probability δ where they remain for an average $1/(\mu+\sigma_1)$ time units. They then progress to the acute h_2 class with probability $\sigma_1/(\mu+\sigma_1)$ where they remain for $1/(\mu+\sigma_2)$ time units. They then move to either the immune class with probability $\sigma_2\alpha/(\mu+\sigma_2)$ where they remain for an average $1/\mu$ time units or the x_1-susceptible class with probability $\sigma_2(1-\alpha)/(\mu+\sigma_2)$ where they again remain for an average $1/\mu$ time units, otherwise they leave the population. Hence

on average an IDU generates

$$\frac{\lambda}{\mu + \sigma_1}$$

acute $h^\dagger$ infectious needles,

$$\frac{\lambda\sigma_1}{(\mu + \sigma_1)(\mu + \sigma_2)}$$

acute h infectious needles, and

$$\frac{\lambda(1-\delta)\sigma_1\sigma_2}{\mu(\mu + \sigma_1)(\mu + \sigma_2)}$$

chronic y infectious needles during their infectious lifetime. We now derive the expected number of IDUs caused by each type of infectious needle until it is no longer infectious. Consider a single acute $h^\dagger$ infectious needle which is used by IDUs at a rate λ. Define $E_{h^\dagger}Y$ to be the number of IDUs infected by a single acute $h^\dagger$ infectious needle, X_1 denote the event that the needle is made safe before the next injection and X_2 denote the event that the needle is still infectious at the time of the next injection, that is it is neither exchanged or cleaned. Therefore

$$E_{h^\dagger}Y = E_{h^\dagger}(Y|X_1)P(X_1) + E_{h^\dagger}(Y|X_2)P(X_2).$$

If the needle is not infectious at the time of the next injection, then it will not infect any IDUs, so $E_{h^\dagger}(Y|X_1) = 0$. The probability of the event X_2 is $\lambda\gamma(1-\phi)/(\lambda\gamma + \tau)$, hence

$$E_{h^\dagger}Y = \frac{\lambda\gamma(1-\phi)}{\lambda\gamma + \tau}E_{h^\dagger}(Y|X_2).$$

We now examine the term $E_{h^\dagger}(Y|X_2)$. Consider a susceptible IDU injecting with an infectious needle. This event has only two possible outcomes: either the IDU is infected by the needle with probability $\alpha_h^\dagger$ or remains susceptible with probability $(1-\alpha_h^\dagger)$. In both cases the needle becomes uninfected and stops infecting IDUs (until it is infected again). Hence the expected number of IDUs infected by a

single acute $h^{\dagger}$ infectious needle is given by

$$E_{h^{\dagger}}Y = \frac{(1-\phi)\alpha_h^{\dagger}}{1+\hat{\tau}}$$

where $\hat{\tau} = \tau/\lambda\gamma$. We use a similar argument to derive the expected number of IDUs that are infected by acute h and chronic y needles until they are not infectious. Multiplying the expected number of infections from each type of infectious needle with the expected number of needles that an IDU generates during their infectious lifetime gives us an expression for the total number of secondary infections caused by a single infectious IDU entering the disease free population. Hence the basic reproductive number is given by

$$R_0 = \frac{\lambda(1-\phi)}{\mu(\mu+\sigma_1)(\mu+\sigma_2)(1+\hat{\tau})}\left[\mu\alpha_h^{\dagger}(\mu+\sigma_2) + \mu\alpha_h\sigma_1 + \alpha_y\sigma_1\sigma_2(1-\delta)\right]. \tag{5.12}$$

Note that if $\sigma_1 \to \infty$ and $\sigma_2 = \sigma$, $R_0 \to \frac{\lambda(1-\phi)}{\mu(\mu+\sigma)(1+\hat{\tau})}[\mu\alpha_h + \alpha_y\sigma(1-\delta)]$. This is what we expect as if σ_1 becomes very large, newly infected IDUs almost immediately enter the acute infectious stage h_1 or h_2 with probabilities $(1-\delta)$ and δ respectively so we are back at the original model. As we expect R_0 for this extended model approaches R_0 for the simple model as σ_1 becomes very large.

We now use the simulation package Berkeley Madonna version 8.3.11 to produce HCV prevalence estimates for the Glasgow IDU population over time given by our model governing equations.

5.5 Simulations

Table 5.1 shows the baseline parameter estimates used in our simulations.

5.5.1 Duration of the acute stages of infection ($1/\sigma_1$, $1/\sigma_2$)

We assume that the total length of time taken for an IDU with continued injecting drug use to progress through the acute stage of HCV infection is six months, where two months are spent in the high infectious phase and four months are spent in

Parameter	Definition	Estimate	Reference	Notes
ϕ	probability of successful needle cleaning	0.255	Unpublished data HPS (1990-1993)	Observational data on Glasgow IDUs during 1990-1993
λ	needle and syringe sharing rate	103 per year	Hutchinson *et al.* (2000)	Observational data on Glasgow IDUs during 1990-1993
τ	needle turnover rate	133 per year	Griesbach *et al.* (2006); King *et al.* (2009)	Observational data for Glasgow during 2004-2005; Posterior mean estimate for Glasgow in 2003
γ	IDU to needle ratio	1.002	Griesbach *et al.* (2006); King *et al.* (2009)	Observational data for Glasgow during 2004-2005; Posterior mean estimate for Glasgow during 2003
μ	rate IDUs leave the sharing population	0.17 per year	Hutchinson, Bird *et al.* (2006)	Model estimate for Glasgow IDUs during 2000
$\alpha_h^\dagger$	highly infectious acute HCV transmission probability	0.0935*		
α_h	acute HCV transmission probability	0.016*		
α_y	chronic HCV transmission probability	0.016*	Vickerman *et al.* (2007)	Model estimate for London IDUs during 2002-2003
$1/\sigma_1$	duration of the highly infectious acute HCV phase	1/6 years	Simmonds *et al.* (1998)	Observational data
$1/\sigma_2$	duration of the acute HCV phase	1/3 years	Simmonds *et al.* (1998)	Observational data
δ	proportion that resolve HCV infection	0.26	Micallef *et al.* (2006)	Review of longitudinal studies from January 1990-April 2003
α	proportion of IDUs** that become immune	0.25	Conservative estimate	No data available

*per shared injection

**who have spontaneously resolved an HCV infection

Table 5.1: Table of baseline parameter estimates.

the low infectious phase. This allows us to estimate $\sigma_1 = 6$ per year and $\sigma_2 = 3$ per year.

5.5.2 Acute HCV transmission probabilities ($\alpha_h^\dagger, \alpha_h$)

We assume that $\alpha_h = \alpha_y$, that is, the transmission probability of the low infectious acute stage equals the transmission probability for the chronic stage of infection. Taking equation (5.12) and substituting in the values for all known parameters except the HCV transmission probabilities gives

$$\begin{aligned} R_0 =& 5.434\alpha_h^\dagger + 10.285\alpha_h + 134.313\alpha_y, \\ =& 5.434\alpha_h^\dagger + 144.598\alpha_h, \quad (\text{since } \alpha_h = \alpha_y). \end{aligned} \tag{5.13}$$

Using (5.13) and selected values for α_h we are able to estimate the value of $\alpha_h^\dagger$ that gives us $R_0 = 2.82$. This is the same value of R_0 we used for our initial HCV model. Thus, if $\alpha_h = 0.016$ then $\alpha_h^\dagger = 0.0935$. We then conduct simulations to examine any differences between the predictions of this model and the simple model.

5.5.3 Numerical results

We can see from Figure 5.2 (where $\alpha_h^\dagger = 0.0935$ and $\alpha_h = 0.016$) that modelling an acute stage where the infectivity is averaged over the length of the acute stage produces a similar endemic equilibrium estimate to that produced by our model where the highly infectious period is explicitly modelled. Further simulations, using a range of values for $\alpha_h^\dagger$ and α_h where $R_0 = 2.82$, show that the long term endemic prevalence of HCV is similar with both models. Furthermore, the results show that $\alpha_h^\dagger = 0.0935$ is almost an exact match to the behaviour suggested by the initial transmission model (Figure 5.2).

Further examination of our model behaviour shows that although the basic reproductive number is the same in all cases, the initial spread of HCV within the population is different (Figure 5.3).

For these simulations we selected values for α_h and α_y, where $\alpha_h = \alpha_y$, either side of our baseline estimate of $\alpha_h = \alpha_y = 0.016$. Then, taking each of these values in turn, we use equation (5.13) to calculate the value of $\alpha_h^\dagger$ that gives us $R_0 = 2.82$.

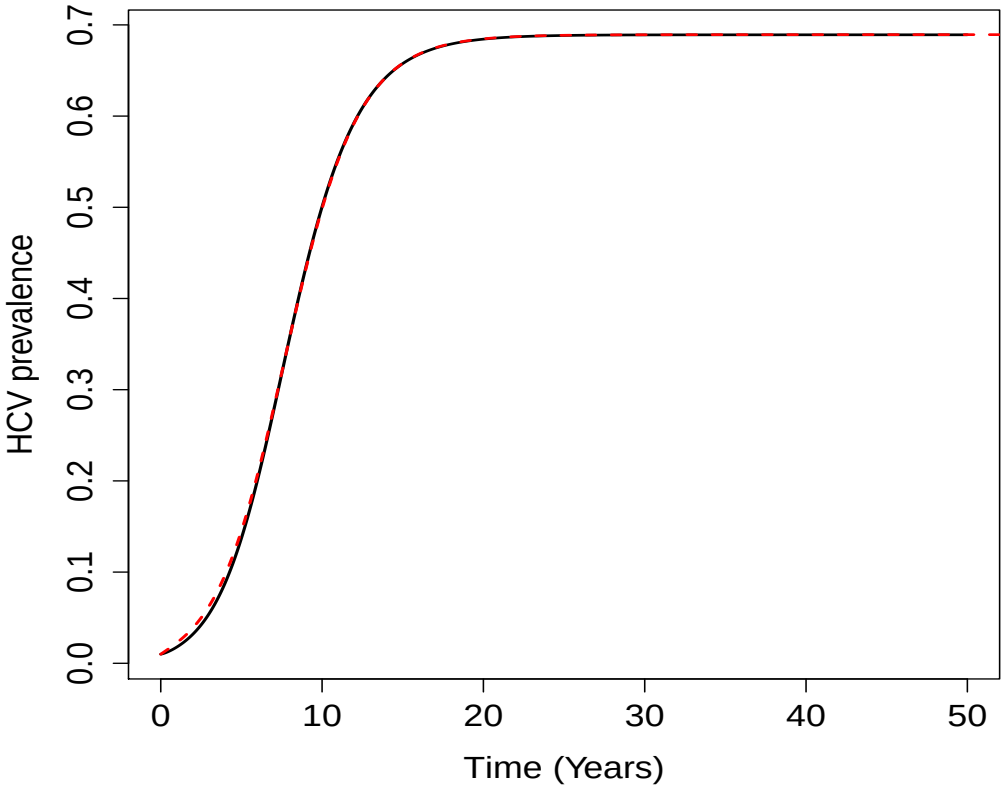

Figure 5.2: HCV prevalence amongst Glasgow IDUs using both the simple model (red dashed line) and the extended model (solid black line).

From this figure we see that increasing $\alpha_h^\dagger$ past $\alpha_h^\dagger = 0.0935$ (blue dotdash line in Figure 5.3) results in faster disease spread, while lowering $\alpha_h^\dagger$ results in slower disease spread. These results are expected since increasing the estimate for $\alpha_h^\dagger$ means that IDUs have a greater risk of contracting and transmitting the virus through needle and syringe sharing.

Recall that for the simple model discussed in Chapter 3, the long term endemic prevalence of HCV amongst IDUs depends on α_h and α_y only through the basic reproductive number R_0. Figure 5.3 also suggests that similarly in this extended model the long term endemic prevalence of HCV amongst IDUs depends on $\alpha_h^\dagger$, α_h and α_y only through R_0.

From these simulations we can conclude that equilibrium prevalence estimates

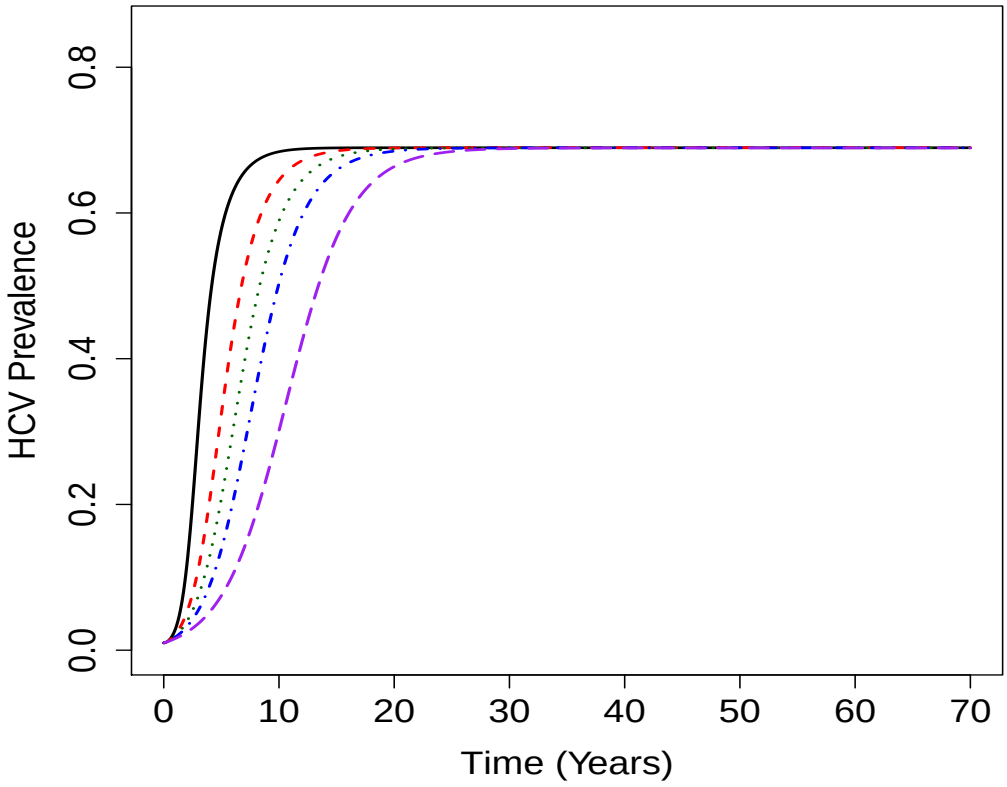

Figure 5.3: HCV prevalence simulations with $(\alpha_h^\dagger, \alpha_h, \alpha_y) = (0.200, 0.012, 0.012)$ (solid black line), (0.147, 0.014, 0.014) (red dashed line), (0.120, 0.015, 0.015) (dotted green line), (0.0935, 0.016, 0.016) (blue dotdash line), (0.040, 0.018, 0.018) (purple long dash line).

are consistent with both model structures and so either can be used to approximate HCV transmission in an IDU population. Both structures, however, highlight the need for accurate estimates of disease transmission probabilities. The changes in behaviour with different transmission probability estimates in our extension model show how important it is for modellers and health organisations to know if a ten-fold increase in infectivity is a correct assumption to make, since an incorrect estimation could result in a faster, or slower, rate of initial HCV spread being predicted.

The effect of this short period of high infectivity has been investigated using a stochastic simulation model developed by Hutchinson, Bird *et al.* (2006), where

simulations of HCV prevalence were obtained both with and without a high infectivity period following seroconversion. The authors assume that the transmission probability per injection of both acute and chronic HCV infection is 2-3% and, when the high infectivity period is employed, the short term transmission probability is 20-30%. Following Hutchinson, Bird *et al.* (2006), we can also model the

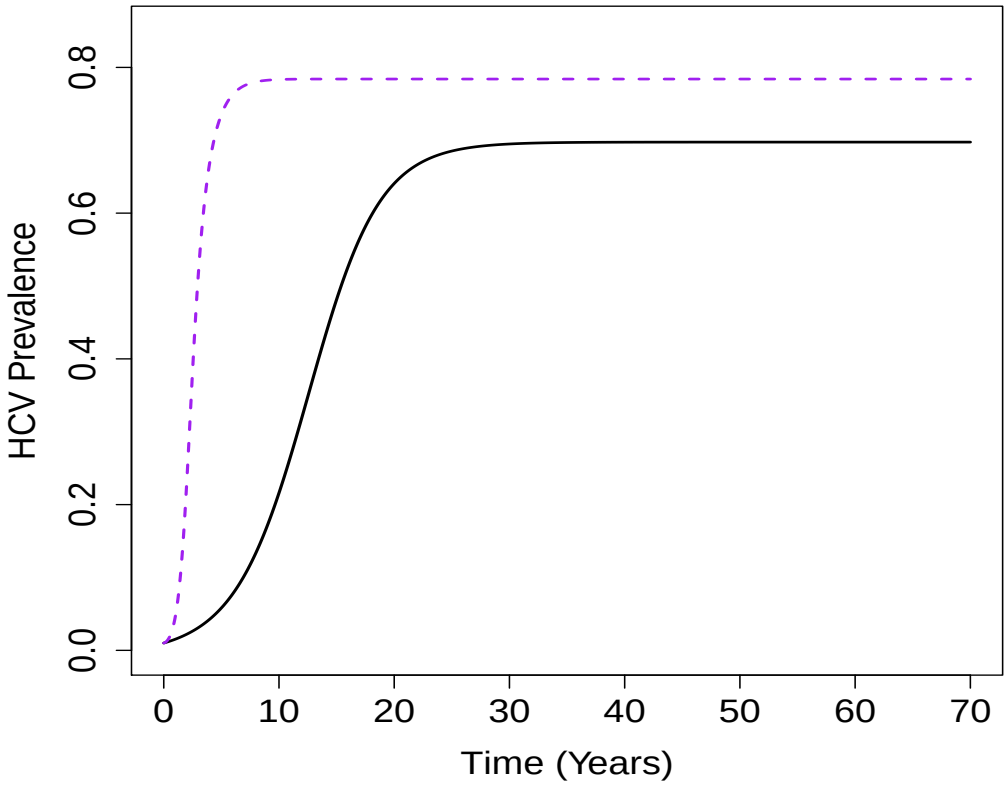

Figure 5.4: HCV prevalence estimates obtained when following the method of Hutchinson, Bird *et al.* (2006) both with (dashed purple line) and without (solid black line) the highly infectious acute phase.

highly infectious acute phase in a similar way. This is shown in Figure 5.4. The solid black line represents the proportion of antibody positive IDUs when we do not model the highly infectious phase (simple HCV transmission model). In line with Hutchinson, Bird *et al.* (2006), we assume that both acute and chronic HCV infectivity (α_h and α_y respectively) are 2%, giving an endemic equilibrium value of approximately 0.70. The upper purple dashed line shows the extended model

behaviour when we incorporate the highly infectious phase, that is $\alpha_h^\dagger = 0.2$, $\alpha_h = \alpha_y = 0.02$. It is clear from this figure that the spread of HCV is faster and the time taken to endemic equilibrium is shorter when we model this highly infectious phase. Furthermore, it can be seen that the endemic equilibrium is 0.784, an increase of 8.4%.

Modelling the highly infectious phase in this way makes a significant difference to long term prevalence estimates as well as the rate of disease spread and the time to endemic equilibrium. This change in model behaviour is because the basic reproductive number has increased from 2.82 to 3.98 when using this method. While our transmission model differs from the stochastic model used by Hutchinson, Bird *et al.* (2006), the long term endemic HCV prevalence estimate (for both methods) is close to the uncertainty interval reported by the authors (62-72%). They also note that, when modelling the highly infectious phase, significantly more simulations produced HCV prevalence estimates in the ranges of those obtained though community-wide surveys of Glasgow IDUs.

5.6 Conclusions

In this section we have shown two different methods for modelling the increase in infectivity at the beginning of the acute phase. This increase in infectivity may be as high as ten-fold. With both methods we have seen an increased rate of disease spread as well as a shorter time to endemic equilibrium, although these were not the same rate in both cases. Our second method, following Hutchinson, Bird *et al.* (2006), resulted in an increase of 8.4% in the endemic equilibrium HCV prevalence in IDUs when modelling the highly infectious phase. The observed increased rate of disease spread is a very important issue for disease control. Increasing the rate of disease spread means that health organisations have less time to employ their control measures and prevent an epidemic. Therefore, to make our models as realistic as possible, more work must be done in understanding the existence of a highly infectious acute phase and how it should be modelled.

This concludes our investigation into the highly infectious acute stage of infection. In the next chapter we will develop another HCV transmission model which incorporates more heterogeneity than the previous models we have examined.

Chapter 6

A time since onset of injection model for HCV spread among IDUs

Injecting drug use is a well documented risk factor for HCV acquisition (van Beek *et al.* 1994; Roy *et al.* 2007, 2009) with HCV prevalences of over 60% recorded in IDU populations (Hope *et al.* 2001; Judd *et al.* 2005). Studies have found a high incidence of HCV infection among recent initiates to injecting drug use (Roy *et al.* 2007; Mehta *et al.* 2011), due to the high risk injecting practices documented in inexperienced injectors (Cassin *et al.* 1998; Hahn *et al.* 2002; Mathei *et al.* 2008). Therefore, the IDU population can potentially be separated by time since onset of injection into two risk groups; naive injectors and experienced injectors with different injecting risk behaviours. Understanding the differences between these two groups and the way that they interact could lead to better allocation of prevention measures and therefore reduce the burden associated with HCV infection. Few studies have modelled the spread of HCV among IDUs in this way and demonstrated the potential effectiveness of interventions such as needle exchange and other harm reduction measures (Kretzschmar and Wiessing 2004; Vickerman *et al.* 2007). However, Sutton *et al.* (2006) used statistical modelling techniques to analyse the saliva samples of 5,682 IDUs in England and Wales who were tested for HBV and HCV from 1998-2003 in order to derive the maximum likelihood estimates of the force of infection for HBV and HCV. Their analysis

suggested that the force of HCV infection for naive IDUs (defined as those who have an injecting career of less than one year) during 1999-2003 (0.1608, 95% CI 0.1314-0.1942) was greater than the force of HCV infection for experienced IDUs for the same period (0.0525, 95% CI 0.0310-0.0863). These figures further support the need to consider a population stratified into naive and experienced risk groups.

Kretzschmar and Wiessing (2004) introduced an HCV transmission model for a hypothetical IDU population that allowed for heterogeneity in needle and syringe sharing rates and discussed an extension of the model by incorporating time since onset of injection. The basic model was a compartmental model which allowed IDUs to progress through four stages of infection: susceptible, acute HCV infection, chronic HCV infection and recovered. IDUs were recruited to the population at a rate B and left the population, due to death, at a per capita rate μ. Once infected with HCV, IDUs progressed to the acute stage of infection. A proportion p of these IDUs developed chronic HCV infection where it was assumed that they could still clear their infection and progress to the recovered class. The remaining proportion $(1-p)$ of the acutely infected IDUs resolved their infection and progressed to the recovered class. IDUs in the recovered class could not be re-infected with HCV and therefore remained in this class until death. The authors simulated the behaviour of the model to investigate how the prevalence of HCV changed when different prevention measures were applied (e.g. reducing the needle and syringe sharing rate). Their results showed that there is a critical sharing rate which when reached results in a steep increase in the prevalence of HCV. The authors then discussed the possibility of extending the model to incorporate time since onset of injection. While the governing equations for the time since onset of injection model are not presented, some numerical results are shown. These results showed that a large fraction of IDUs are infected with HCV within three years of starting injecting (similar to the median 3.3 years reported by Roy *et al.* (2009)), and that for prevention, interventions should aim to change the behaviour of IDUs before they start injecting. Further results showed that after five years, 26% of new injectors and more than 70% of high risk IDUs have chronic HCV.

Vickerman *et al.* (2007) developed a model to simulate the transmission of HCV among London IDUs. The simulations explored the impact of intervention

measures that reduced syringe sharing in (i) all IDUs, (ii) IDUs who had been injecting for more than one year, and (iii) IDUs with either low or high frequencies of sharing. Results showed that large sustained reductions in syringe sharing rates would reduce HCV seroprevalence in IDUs who have been injecting for more than eight years, while modest reductions in syringe sharing would reduce HCV seroprevalence in those IDUs injecting for less than four years. Furthermore, the model results also suggested that interventions had to be aimed at all IDUs and if IDUs were reached within their first year of injecting then large reductions in HCV seroprevalence would be achieved.

In this chapter we develop and analyse a mathematical model that separates our IDU population into two groups (referred to as naive and experienced) by time since onset of injection. We first describe the model and its assumptions that allow IDUs to progress through various stages of HCV infection. Using these assumptions we derive the system of governing equations. Next we derive an expression for the basic reproductive number R_0 before analysing the behaviour of the model mathematically.

6.1 Model description

We use the model structure from Chapter 3 to develop an IDU only model (a model that does not explicitly model needles) that stratifies the IDU population into two risk groups by time since onset of injection. This work is based on models previously described by Greenhalgh (1997), Kretzschmar and Wiessing (2004) and Vickerman *et al.* (2009). In Greenhalgh (1997), the author develops a mathematical model to investigate the effects of heterogeneous mixing on the spread of HIV and AIDS amongst IDUs. While this model cannot be used to model HCV directly, the mechanism whereby IDUs in one group decide to share needles and syringes with IDUs in another group is useful in our HCV model. Kretzschmar and Wiessing (2004) develop an IDU only model where the IDU population is separated into two risk groups: a high risk group and a low risk group, however, the only difference between the groups appears to be the needle and syringe sharing rate. Furthermore, this model does not appear to include harm reduction measures such as needle and syringe cleaning or needle exchange. In contrast to this model, we will separate the IDU population into two risk

groups (naive and experienced) by their time since onset of injection and include measures that allow for the prevention of HCV infection. The model described by Vickerman *et al.* (2009) divides the IDU population by both time since onset of injection and frequency of drug injection. While the authors incorporate evidence supporting a risk of HCV re-infection among IDUs who resolve an infection, it is not clear how IDUs move between the experience classes. Our transmission model modifies this work so that the IDU population is divided solely by time since onset of injection. Furthermore, while Vickerman *et al.* (2009) model the effects of antiviral treatment on HCV prevalence among IDUs, we do not consider this intervention in our model.

We assume that the IDU population is of size n, where n is large and constant. Thus IDUs who cease injecting either due to death or cessation of injecting drug use leave the population at a per capita rate μ and are immediately replaced by IDUs susceptible to HCV infection.

The model allows for several HCV infection stages: those susceptible to infection (denoted x for those not previously infected and x_1 for those previously infected), those acutely infected with HCV (denoted h_1 and h_2), those chronically infected (y) and those immune to HCV re-infection (z) (Figure 6.1). The term f_i, which will be defined later, denotes the force of infection experienced by naive IDUs ($i = 0$) and experienced IDUs ($i = 1$).

When susceptible IDUs are infected with HCV they progress to an acute stage of infection (either h_1 or h_2). A proportion δ of newly infected IDUs will progress to the acute h_2 infected class. At the end of their time in this class these IDUs will either leave the injecting population or spontaneously clear their infection, with a fraction α developing immunity to HCV re-infection and the remaining fraction (1-α) becoming susceptible to HCV re-infection (Farci *et al.* 1992; Mehta *et al.* 2002; Micallef *et al.* 2007). The remaining proportion (1-δ) of newly infected IDUs progress to the acute h_1 infected class which may lead to the development of chronic HCV infection. Chronically infected IDUs are assumed to remain infected until they either die or leave the injecting population.

As well as separating the IDU population by infection status, our model further stratifies the population into two risk groups dependent on whether the IDUs have a long (experienced) or short (naive) injecting career. Each naive IDU moves at a per capita rate η from the naive tier to the experienced tier. In doing so, they

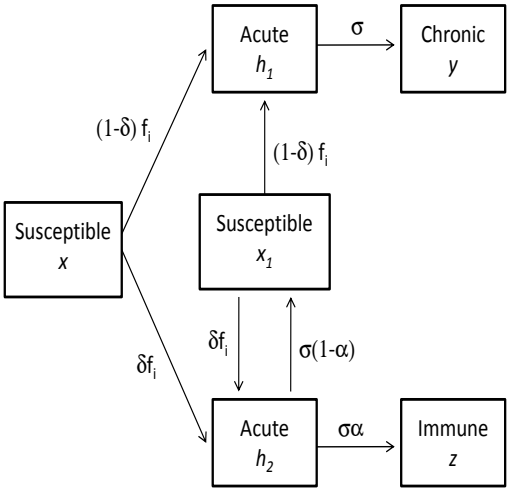

Figure 6.1: Flow diagram for HCV transmission model. The arrows in the diagram indicate the possible transitions for IDUs between stages of HCV infection and the parameters shown are the per capita rate of flow between the stages. The rate of recruitment to the population (μ), the rate at which IDUs leave the population (μ) and the rate at which IDUs move from the naive tier to the experienced tier (η) are not shown.

move into an equivalent model category, specific to their HCV infection status at that time.

6.2 Model derivation

We now derive the differential equations which describe the spread of HCV among IDUs where IDUs progress through the stages of infection described in Section 6.1. We first use techniques used previously to derive a model where both IDUs and needles are modelled explicitly. If we assume that needles can be either naive or experienced (dependent on their last user) and exist in three infectious classes (acute h_1, acute h_2 and chronic y), we will derive a total of 18 differential

equations: 12 equations for IDUs and six for needles. We then derive an IDU only model and show that under certain assumptions these models are equivalent. A total of 12 differential equations will be derived for the IDU only model.

Let $\pi_x^i(t)$, $\pi_{x_1}^i(t)$, $\pi_{h_1}^i(t)$, $\pi_{h_2}^i(t)$, $\pi_y^i(t)$ and $\pi_z^i(t)$ denote the fraction of all IDUs that are respectively in the naive ($i = 0$) or experienced ($i = 1$) x-susceptible, x_1-susceptible, acute h_1, acute h_2, chronic y, immune z infectious classes at time t. In a similar way, $\beta_{h_1}^i(t)$, $\beta_{h_2}^i(t)$ and β_y^i denote the fraction of needles and syringes that were last used by a naive ($i = 0$) or experienced ($i = 1$) user, which are respectively in the acute h_1, acute h_2 and chronic y infectious stages at time t. Furthermore, let λ_i denote the average needle and syringe sharing rate for group i IDUs; ϕ denote the probability that an IDU will successfully clean their needles and syringes prior to use (meaning that IDUs clean their needles and syringes with alcohol or bleach so that there is no HCV viral load present prior to injecting); α_h and α_y denote respectively the transmission probabilities of acute and chronic HCV infection; s_{i0} and s_{i1} represent the fraction of injecting equipment that an IDU in experience group i borrows from naive IDUs and experienced IDUs respectively; and π^0, π^1 denote the fraction of IDUs that are naive and experienced injectors respectively. Note that in order to ensure that our model is realistic, we have put a constraint on s_{01} and s_{10} by ensuring that $\lambda_0 s_{01}\mu = \lambda_1 s_{10}\eta$ (details are given in Appendix A.1). This is necessary to ensure that the number of needles in the two experience groups remains positive. Henceforth, we will assume that this constraint is satisfied.

6.2.1 Governing equations for IDU and needle model

We now derive the equations which describe the behaviour of our IDU population over time.

IDU population

$n\pi_x^0(t+\Delta t)$, the number of naive x-susceptible IDUs at time $t+\Delta t$

$=$ the number of naive x-susceptible IDUs at time t

$+$ the number of IDUs recruited to sharing intravenous injecting drug use in $[t,\ t+\Delta t)$

$-$ the number of naive x-susceptible IDUs who move into the experienced tier of the model in $[t,\ t+\Delta t)$

$-$ the number of naive x-susceptible IDUs who leave the population due to death or cessation of injecting drug use in $[t,\ t+\Delta t)$

$-$ the number of naive x-susceptible IDUs who develop acute HCV infection after borrowing needles and syringes last used by naive IDUs in $[t,\ t+\Delta t)$

$-$ the number of naive x-susceptible IDUs who develop acute HCV infection after borrowing needles and syringes last used by experienced IDUs in $[t,\ t+\Delta t)$.

Thus we have

$$\begin{aligned} n\pi_x^0(t+\Delta t) = {} & n\pi_x^0(t) + n\mu\Delta t - n\Delta t(\mu+\eta)\pi_x^0 \\ & - n\Delta t\lambda_0 s_{00}(1-\phi)\pi_x^0(\alpha_h(\beta_{h_1}^0+\beta_{h_2}^0)+\alpha_y\beta_y^0) \\ & - n\Delta t\lambda_0 s_{01}(1-\phi)\pi_x^0(\alpha_h(\beta_{h_1}^1+\beta_{h_2}^1)+\alpha_y\beta_y^1) + o(\Delta t). \end{aligned}$$

Subtracting $n\pi_x^0(t)$ from both sides, dividing by $n\Delta t$ and letting $\Delta t \to 0$ gives

$$\begin{aligned} \frac{d\pi_x^0}{dt} = {} & \mu - (\mu+\eta)\pi_x^0 - \lambda_0 s_{00}(1-\phi)\pi_x^0(\alpha_h(\beta_{h_1}^0+\beta_{h_2}^0)+\alpha_y\beta_y^0) \\ & - \lambda_0 s_{01}(1-\phi)\pi_x^0(\alpha_h(\beta_{h_1}^1+\beta_{h_2}^1)+\alpha_y\beta_y^1). \end{aligned}$$

$n\pi^0_{x_1}(t+\Delta t)$, the number of naive x_1-susceptible IDUs at time t+Δt

$=$ the number of naive x_1-susceptible IDUs at time t

$+$ the number of naive IDUs who spontaneously resolve an HCV infection in $[t,\ t+\Delta t)$

$-$ the number of naive x_1-susceptible IDUs who move into the experienced tier of the model in $[t,\ t+\Delta t)$

$-$ the number of naive x_1-susceptible IDUs who leave the population due to death or cessation of injecting drug use in $[t,\ t+\Delta t)$

$-$ the number of naive x_1-susceptible IDUs who develop acute HCV infection after borrowing needles and syringes last used by naive IDUs in $[t,\ t+\Delta t)$

$-$ the number of naive x_1-susceptible IDUs who develop acute HCV infection after borrowing needles and syringes last used by experienced IDUs in $[t,\ t+\Delta t)$.

Thus we have

$$\begin{aligned} n\pi^0_{x_1}(t+\Delta t) = {} & n\pi_{x_1}(t) + \sigma(1-\alpha)n\pi^0_{h_2}(t)\Delta t - n(\mu+\eta)\pi^0_{x_1}(t)\Delta t \\ & - n\Delta t\lambda_0 s_{00}(1-\phi)\pi^0_{x_1}(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2})+\alpha_y\beta^0_y) \\ & - n\Delta t\lambda_0 s_{01}(1-\phi)\pi^0_{x_1}(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2})+\alpha_y\beta^1_y) + o(\Delta t). \end{aligned}$$

Subtracting $n\pi_{x_1}(t)$ from both sides, dividing by $n\Delta t$ and letting $\Delta t \to 0$ gives

$$\begin{aligned} \frac{d\pi^0_{x_1}}{dt} = {} & \sigma(1-\alpha)\pi^0_{h_2} - (\mu+\eta)\pi^0_{x_1}(t) \\ & - \lambda_0 s_{00}(1-\phi)\pi^0_{x_1}(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2})+\alpha_y\beta^0_y) \\ & - \lambda_0 s_{01}(1-\phi)\pi^0_{x_1}(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2})+\alpha_y\beta^1_y). \end{aligned}$$

$n\pi^0_{h_1}(t+\Delta t)$, the number of naive acute h_1 infected IDUs at time t+Δt

$=$ the number of naive acute h_1 infected IDUs at time t

$-$ the number of naive acute h_1 IDUs who develop chronic HCV infection in [t, t+Δt)

$-$ the number of naive acute h_1 IDUs who leave the population due to death or cessation of injecting drug use in [t, t+Δt)

$-$ the number of naive acute h_1 IDUs who move into the experienced tier of the model in [t, t+Δt)

$+$ the number of naive susceptible IDUs (both previously infected and previously uninfected) who develop acute h_1 HCV infection after borrowing needles and syringes last used by naive IDUs in [t, t+Δt)

$+$ the number of naive susceptible IDUs (both previously infected and previously uninfected) who develop acute h_1 HCV infection after borrowing needles and syringes last used by experienced IDUs in [t, t+Δt).

Thus we have

$$\begin{aligned} n\pi^0_{h_1}(t+\Delta t) = n\pi^0_{h_1}(t) - n\Delta t(\mu+\sigma+\eta)\pi^0_{h_1}(t) + n\Delta t\lambda_0 s_{00}(1-\phi)(1-\delta) \\ \times \left(\pi^0 - \sum_k \pi^0_k\right)(\alpha_h(\beta^0_{h_1}(t)+\beta^0_{h_2}(t)) + \alpha_y\beta^0_y(t)) + n\Delta t\lambda_0 s_{01}(1-\phi) \\ \times (1-\delta)\left(\pi^0 - \sum_k \pi^0_k\right)(\alpha_h(\beta^1_{h_1}(t)+\beta^1_{h_2}(t)) + \alpha_y\beta^1_y(t)) + o(\Delta t), \end{aligned}$$

where $\sum_k \pi^0_k = \pi^0_{h_1}(t)+\pi^0_{h_2}(t)+\pi^0_y(t)+\pi^0_z(t)$. Subtracting $n\pi^0_{h_1}(t)$ from both sides, dividing by $n\Delta t$ and letting $\Delta t \to 0$ gives

$$\frac{d\pi^0_{h_1}}{dt} = \lambda_0 s_{00}(1-\phi)(1-\delta)\left(\pi^0 - \sum_k \pi^0_k\right)(\alpha_h(\beta^0_{h_1} + \beta^0_{h_2}) + \alpha_y\beta^0_y)$$
$$+ \lambda_0 s_{01}(1-\phi)(1-\delta)\left(\pi^0 - \sum_k \pi^0_k\right)(\alpha_h(\beta^1_{h_1} + \beta^1_{h_2}) + \alpha_y\beta^1_y)$$
$$- (\mu+\sigma+\eta)\pi^0_{h_1}.$$

Similarly for naive acute h_2 infected IDUs we have

$$\frac{d\pi^0_{h_2}}{dt} = \lambda_0 s_{00}(1-\phi)\delta\left(\pi^0 - \sum_k \pi^0_k\right)(\alpha_h(\beta^0_{h_1} + \beta^0_{h_2}) + \alpha_y\beta^0_y)$$
$$+ \lambda_0 s_{01}(1-\phi)\delta\left(\pi^0 - \sum_k \pi^0_k\right)(\alpha_h(\beta^1_{h_1} + \beta^1_{h_2}) + \alpha_y\beta^1_y)$$
$$- (\mu+\sigma+\eta)\pi^0_{h_2}.$$

$n\pi^0_y(t+\Delta t)$, the number of naive chronic y infected IDUs at time t+Δt

- $=$ the number of naive chronically infected IDUs at time t
- $+$ the number of naive acute h_1 infected IDUs that develop chronic HCV HCV infection in [t, t+Δt)
- $-$ the number of chronic cases that leave the population in [t, t+Δt)
- $-$ the number of chronic cases that move into the experienced tier in [t, t+Δt).

Thus we have

$$n\pi^0_y(t+\Delta t) = n\pi^0_y(t) + n\Delta t\pi^0_{h_1}(t)\sigma - \pi^0_y(t)(\mu+\eta)n\Delta t + o(\Delta t).$$

Subtracting $n\pi^0_y(t)$ from both sides, dividing by $n\Delta t$ then letting $\Delta t \to 0$ gives

$$\frac{d\pi^0_y}{dt} = \sigma\pi^0_{h_1} - (\mu+\eta)\pi^0_y.$$

Similarly for naive immune z IDUs we have

$$\frac{d\pi_z^0}{dt} = \sigma\alpha\pi_{h_2}^0 - (\mu+\eta)\pi_z^0.$$

Using similar techniques, we can derive the six equations that describe the behaviour of experienced IDUs at each stage of infection over time. Therefore, the 12 equations that describe the behaviour of all IDUs over time are given by

$$\frac{d\pi_x^0}{dt} = \mu - (\mu+\eta)\pi_x^0 - \overline{f}_0\pi_x^0, \tag{6.1}$$
$$\frac{d\pi_{x_1}^0}{dt} = \sigma(1-\alpha)\pi_{h_2}^0 - (\mu+\eta)\pi_{x_1}^0 - \overline{f}_0\pi_{x_1}^0, \tag{6.2}$$
$$\frac{d\pi_{h_1}^0}{dt} = (1-\delta)\overline{f}_0(\pi^0 - \pi_{h_1}^0 - \pi_{h_2}^0 - \pi_y^0 - \pi_z^0) - (\mu+\sigma+\eta)\pi_{h_1}^0, \tag{6.3}$$
$$\frac{d\pi_{h_2}^0}{dt} = \delta\overline{f}_0(\pi^0 - \pi_{h_1}^0 - \pi_{h_2}^0 - \pi_y^0 - \pi_z^0) - (\mu+\sigma+\eta)\pi_{h_2}^0, \tag{6.4}$$
$$\frac{d\pi_y^0}{dt} = \sigma\pi_{h_1}^0 - (\mu+\eta)\pi_y^0, \tag{6.5}$$
$$\frac{d\pi_z^0}{dt} = \sigma\alpha\pi_{h_2}^0 - (\mu+\eta)\pi_z^0, \tag{6.6}$$
$$\frac{d\pi_x^1}{dt} = \eta\pi_x^0 - \mu\pi_x^1 - \overline{f}_1\pi_x^1, \tag{6.7}$$
$$\frac{d\pi_{x_1}^1}{dt} = \eta\pi_{x_1}^0 + \sigma(1-\alpha)\pi_{h_2}^1 - \mu\pi_{x_1}^1 - \overline{f}_1\pi_{x_1}^1, \tag{6.8}$$
$$\frac{d\pi_{h_1}^1}{dt} = \eta\pi_{h_1}^0 + (1-\delta)\overline{f}_1(\pi^1 - \pi_{h_1}^1 - \pi_{h_2}^1 - \pi_y^1 - \pi_z^1) - (\mu+\sigma)\pi_{h_1}^1, \tag{6.9}$$
$$\frac{d\pi_{h_2}^1}{dt} = \eta\pi_{h_2}^0 + \delta\overline{f}_1(\pi^1 - \pi_{h_1}^1 - \pi_{h_2}^1 - \pi_y^1 - \pi_z^1) - (\mu+\sigma)\pi_{h_2}^1, \tag{6.10}$$
$$\frac{d\pi_y^1}{dt} = \eta\pi_y^0 + \sigma\pi_{h_1}^1 - \mu\pi_y^1, \tag{6.11}$$
$$\frac{d\pi_z^1}{dt} = \eta\pi_z^0 + \sigma\alpha\pi_{h_2}^1 - \mu\pi_z^1, \tag{6.12}$$

where $\pi_j^i \geq 0$, $\sum_j \pi_j^0 + \sum_j \pi_j^1 = 1$ $(j = x, x_1, h_1, h_2, y, z)$ and $\overline{f}_0$, $\overline{f}_1$ are given by $\overline{f}_i = \lambda_i(1-\phi)s_{i0}\big(\alpha_h(\beta_{h_1}^0 + \beta_{h_2}^0) + \alpha_y\beta_y^0\big) + \lambda_i(1-\phi)s_{i1}\big(\alpha_h(\beta_{h_1}^1 + \beta_{h_2}^1) + \alpha_y\beta_y^1\big)$. Equations (6.1)-(6.6) describe how the behaviour of naive IDUs at each stage of HCV infection changes over time while equations (6.7)-(6.12) describe how the

behaviour of experienced IDUs at each infectious stage over time.

Needles and syringes

We now derive equations that describe how the fraction of needles and syringes at each stage of infection changes over time. We define m_0 to be the number of naive needles and syringes in circulation. By naive needles and syringes we mean needles and syringes which were either last used by a naive IDU or are the last in a sequence of unused exchanged needles and syringes, the first of which was exchanged for a needle and syringe last used by a naive IDU. If for simplicity of exposition we assume that all IDUs borrow needles and syringes immediately before they inject then the group of naive needles and syringes is exactly those needles and syringes in circulation in the current possession of a naive IDU. We similarly define m_1 to be the number of experienced needles and syringes in circulation. We define $\Lambda_{jk} = \frac{\lambda_j s_{jk} n_j}{m_k}$, $j, k = 0, 1$, to be the rate at which an IDU in group j picks up a needle and syringe last used by a group k IDU.

$m_0\beta^0_{h_1}(t + \Delta t)$, the number of naive acute h_1 infected needles at time t+Δt

$=$ the number of acute h_1 infected needles and syringes at time t

$+$ (the number of naive non acute h_1 infected needles and syringes at time t) $\times$ (the fraction used by naive acute h_1 IDUs in [t, t+Δt))

$-$ (the number of naive acute h_1 infected needles and syringes at time t) $\times$ (the fraction used by naive non acute h_1 IDUs in [t, t+Δt))

$+$ the number of experienced needles and syringes at time t used by a naive acute h_1 infected IDU in [t, t+Δt)

$-$ the number of naive acute h_1 needles and syringes used by experienced IDUs in [t, t+Δt)

$-$ the number of naive acute h_1 needles and syringes exchanged in [t, t+Δt).

Thus we have

$$m_0\beta^0_{h_1}(t+\Delta t) = m_0\beta^0_{h_1}(t) + \Lambda_{00}\left(\frac{\pi^0_{h_1}}{\pi^0}m_0\big(1-\beta^0_{h_1}\big) - \frac{\pi^0-\pi^0_{h_1}}{\pi^0}m_0\beta^0_{h_1}\right)\Delta t$$
$$+ \Lambda_{01}\frac{\pi^0_{h_1}}{\pi^0}m_1\Delta t - \Lambda_{10}m_0\beta^0_{h_1}\Delta t - m_0\beta^0_{h_1}\tau\Delta t + o(\Delta t).$$

Subtracting $m_0\beta^0_{h_1}(t)$ from both sides, dividing by Δt then letting $\Delta t \to 0$ gives

$$m_0\frac{d\beta^0_{h_1}}{dt} = \big(m_0\Lambda_{00} + m_1\Lambda_{01}\big)\frac{\pi^0_{h_1}}{\pi^0} - m_0(\Lambda_{00}+\Lambda_{10}+\tau)\beta^0_{h_1}. \tag{6.13}$$

Similarly, for the other infectious needle groups we have

$$m_0\frac{d\beta^0_{h_2}}{dt} = \big(m_0\Lambda_{00} + m_1\Lambda_{01}\big)\frac{\pi^0_{h_2}}{\pi^0} - m_0(\Lambda_{00}+\Lambda_{10}+\tau)\beta^0_{h_2}, \tag{6.14}$$
$$m_0\frac{d\beta^0_{y}}{dt} = \big(m_0\Lambda_{00} + m_1\Lambda_{01}\big)\frac{\pi^0_{y}}{\pi^0} - m_0(\Lambda_{00}+\Lambda_{10}+\tau)\beta^0_{y}, \tag{6.15}$$
$$m_1\frac{d\beta^1_{h_1}}{dt} = \big(m_1\Lambda_{11} + m_0\Lambda_{10}\big)\frac{\pi^1_{h_1}}{\pi^1} - m_1(\Lambda_{11}+\Lambda_{01}+\tau)\beta^1_{h_1}, \tag{6.16}$$
$$m_1\frac{d\beta^1_{h_2}}{dt} = \big(m_1\Lambda_{11} + m_0\Lambda_{10}\big)\frac{\pi^1_{h_2}}{\pi^1} - m_1(\Lambda_{11}+\Lambda_{01}+\tau)\beta^1_{h_1}, \tag{6.17}$$
$$m_1\frac{d\beta^1_{y}}{dt} = \big(m_1\Lambda_{11} + m_0\Lambda_{10}\big)\frac{\pi^1_{y}}{\pi^1} - m_1(\Lambda_{11}+\Lambda_{01}+\tau)\beta^1_{y}, \tag{6.18}$$

with appropriate initial conditions. Therefore, the governing equations for the IDU and needle time since onset of injection model are given by equations (6.1)-(6.18). This model contains 18 governing equations which makes it very difficult to perform any kind of mathematical analysis. Another way to model the spread of HCV in our population is to develop an IDU only model. The approximation argument that was used in the local stability analysis of the endemic equilibrium of the simple model (Theorem 3.5) shows that it is possible to have an approximately valid IDU only model which has the same basic reproductive number and equilibrium values as the full model. In slightly different situations Kretzschmar and Wiessing (2004) and Vickerman *et al.* (2009) model only IDUs and the same argument can be used to justify their models. We will now develop an IDU only model based on the model of Kretzschmar and Wiessing (2004).

6.3 IDU only model

We now develop our IDU only model. We first derive the equations which govern the behaviour of our IDU population over time. We will then use an approximation technique to show that this model is equivalent to the IDU and needle model that we have just developed.

The number of naive x-susceptible IDUs at time $t+\Delta t$

= the number of naive x susceptible IDUs at time t
+ the number of newly initiated IDUs in $[t,\ t+\Delta t)$
− the number of naive x-susceptible IDUs who leave the population due to death or cessation of injecting drug use and the number of IDUs who progress from the naive tier to the experienced tier in $[t,\ t+\Delta t)$
− the number of naive x-susceptible IDUs who develop acute HCV infection after borrowing injecting equipment from other naive IDUs in $[t,\ t+\Delta t)$
− the number of naive x-susceptible IDUs who develop acute HCV infection after borrowing injecting equipment from experienced IDUs in $[t,\ t+\Delta t)$.

Therefore, we have

$$\begin{aligned} n\pi_x^0(t+\Delta t) = \ & n\pi_x^0(t) + n\mu\Delta t - n\Delta t(\mu+\eta)\pi_x^0 \\ & - n\Delta t\lambda_0(1-\phi)s_{00}\frac{\psi_0}{\pi^0}\big(\alpha_h(\pi_{h_1}^0+\pi_{h_2}^0)+\alpha_y\pi_y^0\big)\pi_x^0 \\ & - n\Delta t\lambda_0(1-\phi)s_{01}\frac{\psi_1}{\pi^1}\big(\alpha_h(\pi_{h_1}^1+\pi_{h_2}^1)+\alpha_y\pi_y^1\big)\pi_x^0 + o(\Delta t). \end{aligned}$$

Here, $\psi_0(t)$ and $\psi_1(t)$ are the probabilities at time t of choosing an unexchanged needle and syringe from the naive and experienced needles and syringes respectively and are given by

$$\psi_0 = \frac{\Lambda_{00}+\Lambda_{10}}{(\Lambda_{00}+\Lambda_{10}+\tau)}, \quad \psi_1 = \frac{\Lambda_{11}+\Lambda_{01}}{(\Lambda_{11}+\Lambda_{01}+\tau)}. \tag{6.19}$$

The derivation of these terms can be found in Appendix A.2. Subtracting $n\pi_x^0(t)$

from both sides, dividing by $n\Delta t$ and letting $\Delta t \to 0$ gives

$$\begin{aligned}\frac{d\pi_x^0}{dt} = \; & \mu - (\mu+\eta)\pi_x^0 - \lambda_0(1-\phi)s_{00}\frac{\psi_0}{\pi^0}\big(\alpha_h(\pi_{h_1}^0+\pi_{h_2}^0)+\alpha_y\pi_y^0\big)\pi_x^0 \\ & - \lambda_0(1-\phi)s_{01}\frac{\psi_1}{\pi^1}\big(\alpha_h(\pi_{h_1}^1+\pi_{h_2}^1)+\alpha_y\pi_y^1\big)\pi_x^0.\end{aligned}$$

Using a similar procedure we can derive the other 11 differential equations for this IDU only model. Hence the system of equations which govern the behaviour of the model is given by

$$\frac{d\pi_x^0}{dt} = \mu - (\mu+\eta)\pi_x^0 - f_0\pi_x^0, \tag{6.20}$$

$$\frac{d\pi_{x_1}^0}{dt} = \sigma(1-\alpha)\pi_{h_2}^0 - (\mu+\eta)\pi_{x_1}^0 - f_0\pi_{x_1}^0, \tag{6.21}$$

$$\frac{d\pi_{h_1}^0}{dt} = (1-\delta)f_0(\pi^0 - \pi_{h_1}^0 - \pi_{h_2}^0 - \pi_y^0 - \pi_z^0) - (\mu+\sigma+\eta)\pi_{h_1}^0, \tag{6.22}$$

$$\frac{d\pi_{h_2}^0}{dt} = \delta f_0(\pi^0 - \pi_{h_1}^0 - \pi_{h_2}^0 - \pi_y^0 - \pi_z^0) - (\mu+\sigma+\eta)\pi_{h_2}^0, \tag{6.23}$$

$$\frac{d\pi_y^0}{dt} = \sigma\pi_{h_1}^0 - (\mu+\eta)\pi_y^0, \tag{6.24}$$

$$\frac{d\pi_z^0}{dt} = \sigma\alpha\pi_{h_2}^0 - (\mu+\eta)\pi_z^0, \tag{6.25}$$

$$\frac{d\pi_x^1}{dt} = \eta\pi_x^0 - \mu\pi_x^1 - f_1\pi_x^1, \tag{6.26}$$

$$\frac{d\pi_{x_1}^1}{dt} = \eta\pi_{x_1}^0 + \sigma(1-\alpha)\pi_{h_2}^1 - \mu\pi_{x_1}^1 - f_1\pi_{x_1}^1, \tag{6.27}$$

$$\frac{d\pi_{h_1}^1}{dt} = \eta\pi_{h_1}^0 + f_1(1-\delta)(\pi^1 - \pi_{h_1}^1 - \pi_{h_2}^1 - \pi_y^1 - \pi_z^1) - (\mu+\sigma)\pi_{h_1}^1, \tag{6.28}$$

$$\frac{d\pi_{h_2}^1}{dt} = \eta\pi_{h_2}^0 + \delta f_1(\pi^1 - \pi_{h_1}^1 - \pi_{h_2}^1 - \pi_y^1 - \pi_z^1) - (\mu+\sigma)\pi_{h_2}^1, \tag{6.29}$$

$$\frac{d\pi_y^1}{dt} = \eta\pi_y^0 + \sigma\pi_{h_1}^1 - \mu\pi_y^1, \tag{6.30}$$

$$\frac{d\pi_z^1}{dt} = \eta\pi_z^0 + \sigma\alpha\pi_{h_2}^1 - \mu\pi_z^1, \tag{6.31}$$

where $\pi_j^i \geq 0$, $\sum_j \pi_j^0 + \sum_j \pi_j^1 = 1$ $(j = x, x_1, h_1, h_2, y, z)$ and f_0, f_1 are given by $f_i = \lambda_i(1-\phi)s_{i0}\frac{\psi_0}{\pi^0}\big(\alpha_h(\pi_{h_1}^0+\pi_{h_2}^0)+\alpha_y\pi_y^0\big) + \lambda_i(1-\phi)s_{i1}\frac{\psi_1}{\pi^1}\big(\alpha_h(\pi_{h_1}^1+\pi_{h_2}^1)+\alpha_y\pi_y^1\big)$. Equations (6.20)-(6.25) describe how the behaviour of naive IDUs at each stage

of HCV infection changes over time while equations (6.26)-(6.31) describe how the behaviour of experienced IDUs at each infectious stage changes over time.

It is possible to show that the model given by equations (6.1)-(6.18) is equivalent to the IDU only model given by equations (6.20)-(6.31). In our analysis of the local stability of the endemic equilibrium in the simple model we approximated the dynamic relationship between the IDU and needle classes by observing that an IDU injects on a timescale that is in the order of days whereas the epidemiological and demographic changes are much slower and measured in years. Examining equation (6.13) we can see that if the prevalence of HCV is constant among each group of the IDU population, and the size of the naive IDU group and the two needle population group sizes are constant then HCV prevalence in the $\beta^0_{h_1}$ group of needles will tend to

$$\frac{m_0\Lambda_{00} + m_1\Lambda_{01}}{m_0(\Lambda_{00} + \Lambda_{10} + \tau)}\frac{\pi^0_{h_1}}{\pi^0} = \frac{\Lambda_{00} + \Lambda_{10}}{(\Lambda_{00} + \Lambda_{10} + \tau)}\frac{\pi^0_{h_1}}{\pi^0}, \quad \text{(using (A.3))}, \tag{6.32}$$

and we can approximate $\beta^0_{h_1}$ by this limiting value. Using equations (6.14)-(6.18) we can obtain similar expressions for the other needle classes:

$$\beta^0_{h_2} \approx \frac{\Lambda_{00} + \Lambda_{10}}{(\Lambda_{00} + \Lambda_{10} + \tau)}\frac{\pi^0_{h_2}}{\pi^0}, \tag{6.33}$$

$$\beta^0_{y} \approx \frac{\Lambda_{00} + \Lambda_{10}}{(\Lambda_{00} + \Lambda_{10} + \tau)}\frac{\pi^0_{y}}{\pi^0}, \tag{6.34}$$

$$\beta^1_{h_1} \approx \frac{\Lambda_{11} + \Lambda_{01}}{(\Lambda_{11} + \Lambda_{01} + \tau)}\frac{\pi^1_{h_1}}{\pi^1}, \tag{6.35}$$

$$\beta^1_{h_2} \approx \frac{\Lambda_{11} + \Lambda_{01}}{(\Lambda_{11} + \Lambda_{01} + \tau)}\frac{\pi^1_{h_2}}{\pi^1}, \tag{6.36}$$

$$\beta^1_{y} \approx \frac{\Lambda_{11} + \Lambda_{01}}{(\Lambda_{11} + \Lambda_{01} + \tau)}\frac{\pi^1_{y}}{\pi^1}. \tag{6.37}$$

Substituting (6.32)-(6.37) into equations (6.1)-(6.12) allows us to re-derive equations (6.20)-(6.31) (see Appendix A.3 for details). Since we have shown that the IDU and needle model can be realistically approximated by the IDU only model we can make our assumption with confidence and as a result we can work with the smaller system given by equations (6.20)-(6.31). This approach is similar to

that used by Vickerman *et al.* (2009).

6.4 The basic reproductive number

The basic reproductive number (R_0) is defined as the expected number of secondary cases per primary case in a "virgin" population (Diekmann and Heesterbeek 2000). Here "virgin" population means that the population is at the DFE when the initial infectious case is introduced. This number is of critical importance in epidemiological models with the disease usually dying out when $R_0 < 1$ and an epidemic usually occurring when $R_0 > 1$. In order to derive the basic reproductive number for our transmission model we consider two cases:

1. The initial infection occurs in a single naive IDU.

2. The initial infection occurs in a single experienced IDU.

As we suppose that the population has reached the DFE both the populations of naive and experienced users and naive and experienced needles and syringes can be assumed to have reached their equilibrium values.

Case 1. Once infected with HCV this individual will progress to the acute h_1 stage of infection with probability $(1-\delta)$ where they remain for an average $1/(\mu+\sigma+\eta)$ time units. They then either

(i) progress to the chronic y stage of infection with probability $\sigma/(\mu+\sigma+\eta)$ where they stay for an average $1/(\mu+\eta)$ time units. They then leave the population with probability $\mu/(\mu+\eta)$ or they move into the experienced chronic class with probability $\eta/(\mu+\eta)$ where they remain for an average $1/\mu$ time units;

(ii) move to the experienced acute h_1 class with probability $\eta/(\mu+\sigma+\eta)$ where they remain for an average $1/(\mu+\sigma)$ time units. They will then leave the injecting population with probability $\mu/(\mu+\sigma)$ or move to the experienced chronic class with probability $\sigma/(\mu+\sigma)$ where they remain for an average $1/\mu$ time units until they eventually leave the sharing, injecting population;

(iii) immediately leave the injecting population with probability $\mu/(\mu+\sigma+\eta)$.

This individual, when infected, can also progress to the acute h_2 stage of infection with probability δ where they remain for an average $1/(\mu+\sigma+\eta)$ time units. They then either

(i) progress to the naive x_1-susceptible class with probability $\sigma(1-\alpha)/(\mu+\sigma+\eta)$ where they remain for an average $1/(\mu+\eta)$ time units. They then leave the injecting population or progress to the experienced x_1-susceptible class, however, in either way they will not infect anyone further since they are the only infected individual present;

(ii) progress to the z-immune class with probability $\sigma\alpha/(\mu+\sigma+\eta)$ but again they will not infect anyone else;

(iii) leave the injecting population with probability $\mu/(\mu+\sigma+\eta)$ and again they will not infect anyone else;

(iv) move into the experienced acute h_2 class with probability $\eta/(\mu+\sigma+\eta)$ where they remain for an average $1/(\mu+\sigma)$ time units before either leaving the injecting population or progressing to either the experienced x_1-susceptible or the experienced z-immune class, either way they will not infect anyone else.

Case 2. Once infected this individual progresses to the acute h_1 stage of infection with probability $(1-\delta)$ where they remain for an average $1/(\mu+\sigma)$ time units. They then either

(i) progress to the chronic stage with probability $\sigma/(\mu+\sigma)$ where they remain for an average $1/\mu$ time units, before leaving the injecting population;

(ii) leave the injecting population with probability $\mu/(\mu+\sigma)$.

This individual can also progress to the acute h_2 stage of infection with probability δ where they remain for an average $1/(\mu+\sigma)$ time units. They then either

(i) progress to the experienced x_1-susceptible class with probability $\sigma(1-\alpha)/(\mu+\sigma)$ where they remain for an average $1/\mu$ time units before

leaving the injecting population. However, they will not infect anyone else as they are the only infected individual present;

(ii) progress to the experienced immune z class with probability $\sigma\alpha/(\mu+\sigma)$ but again they will not infect anyone else;

(iii) immediately leave the injecting population with probability $\mu/(\mu+\sigma)$ and again they will not infect anyone else.

Let κ_{ij} denote the total number of secondary cases caused in the group j by an index case in group i. Then

$$\begin{aligned}
\kappa_{00} &= \text{the expected total number of secondary cases caused in the naive group by a single naive individual} \\
&= \text{the expected total number of secondary cases caused in the naive group by an individual who progresses though the various infectious stages starting at the acute } h_2 \text{ stage of infection} \\
&+ \text{the expected total number of secondary cases caused in the naive group by an individual who progresses through the various infectious stages starting at the acute } h_1 \text{ stage of infection.}
\end{aligned}$$

Let ψ_0^* and ψ_1^* denote the values of ψ_0 and ψ_1 respectively at the DFE. Then

$$\begin{aligned}
\kappa_{00} = \delta\Bigg[&\alpha_h\lambda_0 s_{00}(1-\phi)\psi_0^*\frac{1}{(\mu+\sigma+\eta)} \\
&+ \alpha_h\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\frac{\eta}{(\mu+\sigma+\eta)}\frac{1}{(\mu+\sigma)}\Bigg], \\
+ (1-\delta)\Bigg[&\lambda_0\alpha_h s_{00}(1-\phi)\psi_0^*\frac{1}{(\mu+\sigma+\eta)} \\
&+ \alpha_y\lambda_0 s_{00}(1-\phi)\psi_0^*\frac{\sigma}{(\mu+\sigma+\eta)}\frac{1}{(\mu+\eta)} \\
&+ \alpha_y\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\frac{\sigma}{(\mu+\sigma+\eta)}\frac{\eta}{(\mu+\eta)}\frac{1}{\mu} \\
&+ \alpha_h\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\frac{\eta}{(\mu+\sigma+\eta)}\frac{1}{(\mu+\sigma)} \\
&+ \alpha_y\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\frac{\eta}{(\mu+\sigma+\eta)}\frac{\sigma}{(\mu+\sigma)}\frac{1}{\mu}\Bigg],
\end{aligned}$$

$$
\begin{aligned}
&= \alpha_h \lambda_0 s_{00}(1-\phi)\psi_0^* \frac{1}{(\mu+\sigma+\eta)} + \alpha_y \lambda_0 s_{00}(1-\phi)\psi_0^* \frac{\sigma(1-\delta)}{(\mu+\sigma+\eta)(\mu+\eta)} \\
&+ \alpha_h \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{\eta}{(\mu+\sigma+\eta)(\mu+\sigma)} \\
&+ \alpha_y \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{\eta(1-\delta)\sigma}{\mu(\mu+\sigma+\eta)(\mu+\eta)} \\
&+ \alpha_y \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{\eta\sigma(1-\delta)}{\mu(\mu+\sigma+\eta)(\mu+\sigma)},
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{\lambda_0 s_{00}(1-\phi)\psi_0^*}{(\mu+\sigma+\eta)} \left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{(\mu+\eta)} \right] \\
&+ \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0^*}}{\pi^{1^*}} \frac{\eta}{(\mu+\sigma+\eta)} \left[\frac{\alpha_h}{\mu+\sigma} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\sigma)} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)} \right].
\end{aligned} \tag{6.38}
$$

Similarly, the other κ_{ij} combinations are given by:

$$
\begin{aligned}
\kappa_{01} = \delta \Bigg[& \alpha_h \lambda_1 s_{10}(1-\phi)\psi_0^* \frac{\pi^{1*}}{\pi^{0*}} \frac{1}{(\mu+\sigma+\eta)} \\
& + \alpha_h \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\eta}{(\mu+\sigma+\eta)} \frac{1}{(\mu+\sigma)} \Bigg], \\
+ (1-\delta) \Bigg[& \lambda_1 \alpha_h s_{10}(1-\phi)\psi_0^* \frac{\pi^{1*}}{\pi^{0*}} \frac{1}{(\mu+\sigma+\eta)} \\
& + \alpha_y \lambda_1 s_{10}(1-\phi)\psi_0^* \frac{\pi^{1*}}{\pi^{0*}} \frac{\sigma}{(\mu+\sigma+\eta)} \frac{1}{(\mu+\eta)} \\
& + \alpha_y \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\sigma}{(\mu+\sigma+\eta)} \frac{\eta}{\mu(\mu+\eta)} \\
& + \alpha_h \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\eta}{(\mu+\sigma+\eta)} \frac{1}{(\mu+\sigma)} \\
& + \alpha_y \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\eta}{(\mu+\sigma+\eta)} \frac{\sigma}{\mu(\mu+\sigma)} \Bigg],
\end{aligned}
$$

$$
\begin{aligned}
&= \alpha_h \lambda_1 s_{10}(1-\phi)\psi_0^* \frac{\pi^{1*}}{\pi^{0*}} \frac{1}{(\mu+\sigma+\eta)} + \alpha_h \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\eta}{(\mu+\sigma+\eta)(\mu+\sigma)} \\
&+ \alpha_y \lambda_1 s_{10}(1-\phi)(1-\delta)\psi_0^* \frac{\pi^{1*}}{\pi^{0*}} \frac{\sigma}{(\mu+\sigma+\eta)(\mu+\eta)} \\
&+ \alpha_y \lambda_1 s_{11}(1-\phi)(1-\delta)\psi_1^* \frac{\sigma\eta}{\mu(\mu+\sigma+\eta)(\mu+\eta)} \\
&+ \alpha_y \lambda_1 s_{11}(1-\phi)(1-\delta)\psi_1^* \frac{\sigma\eta}{\mu(\mu+\sigma+\eta)(\mu+\sigma)},
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{\lambda_1 s_{10}(1-\phi)\psi_0^*}{(\mu+\sigma+\eta)} \frac{\pi^{1*}}{\pi^{0*}} \left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{(\mu+\eta)}\right] \\
&+ \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\eta}{(\mu+\sigma+\eta)} \left[\frac{\alpha_h}{\mu+\sigma} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\sigma)}\right].
\end{aligned} \tag{6.39}
$$

$$
\begin{aligned}
\kappa_{10} &= \delta\left[\alpha_h \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{1}{(\mu+\sigma)}\right] \\
&+ (1-\delta)\left[\lambda_0 \alpha_h s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{1}{(\mu+\sigma)} + \alpha_y \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{\sigma}{\mu(\mu+\sigma)}\right],
\end{aligned}
$$

$$
= \frac{\lambda_0 s_{01}(1-\phi)\psi_1^*}{(\mu+\sigma)} \frac{\pi^{0*}}{\pi^{1*}} \left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right]. \tag{6.40}
$$

$$
\begin{aligned}
\kappa_{11} &= \delta\left[\alpha_h \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{1}{(\mu+\sigma)}\right] \\
&+ (1-\delta)\left[\lambda_1 \alpha_h s_{11}(1-\phi)\psi_1^* \frac{1}{(\mu+\sigma)} + \alpha_y \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\sigma}{\mu(\mu+\sigma)}\right], \\
&= \frac{\lambda_1 s_{11}(1-\phi)\psi_1^*}{(\mu+\sigma)} \left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right].
\end{aligned} \tag{6.41}
$$

Equations (6.38)-(6.41) tell us the elements of the next generation matrix which is given by

$$
\begin{bmatrix} \kappa_{00} & \kappa_{01} \\ \kappa_{10} & \kappa_{11} \end{bmatrix}. \tag{6.42}
$$

Theorem 5.3 from Diekmann and Heesterbeek (2000) states that the spectral radius, R_0, of (6.42) is given by the dominant eigenvalue of the matrix. If $\boldsymbol{e}$=[e_1,

$e_2]$ denotes the unique strictly positive eigenvector corresponding to R_0 (using the Perron-Frobenius Theorem, see Meyer (2000)) then

$$\begin{bmatrix} \kappa_{00} & \kappa_{01} \\ \kappa_{10} & \kappa_{11} \end{bmatrix} \begin{bmatrix} e_1 \\ e_2 \end{bmatrix} = R_0 \begin{bmatrix} e_1 \\ e_2 \end{bmatrix}.$$

This can be re-arranged to give

$$\begin{bmatrix} \kappa_{00} - R_0 & \kappa_{01} \\ \kappa_{10} & \kappa_{11} - R_0 \end{bmatrix} \begin{bmatrix} e_1 \\ e_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

Hence for non-trivial solutions we require $(\kappa_{00} - R_0)(\kappa_{11} - R_0) - \kappa_{01}\kappa_{10} = 0$. This quadratic in R_0 has two solutions, the largest of which will equal the spectral radius. It is straightforward to show that the spectral radius is given by

$$R_0 = \frac{1}{2}(\kappa_{00} + \kappa_{11}) + \frac{1}{2}\sqrt{(\kappa_{00} + \kappa_{11})^2 - 4(\kappa_{00}\kappa_{11} - \kappa_{10}\kappa_{01})}, \tag{6.43}$$

with κ_{00}, κ_{01}, κ_{10} and κ_{11} are given by (6.38), (6.39), (6.40) and (6.41) respectively. We now examine the behaviour of the IDU only model analytically.

6.5 Analytical results

In this section we analyse the behaviour of our transmission model. As in Section 3.4, we will perform an equilibrium and stability analysis in order to determine the nature of any equilibrium solutions. We will show that when $R_0 \leq 1$ the only non-negative solution to our system of equations is the disease free solution. In addition, we shall show that when $R_0 > 1$ there exists a unique non-zero equilibrium solution. A global stability analysis will show that the DFE is globally asymptotically stable if $R_0 \leq 1$.

As with our previous analysis, we assume that the probability of successful needle and syringe cleaning, ϕ, lies between zero and one but cannot take the value one and that all other model parameters are strictly positive with $\delta < 1$.

Let π_j^{i*}, $j = h_1, h_2, y, z$ denote the endemic equilibrium proportions of naive ($i = 0$) and experienced ($i = 1$) IDUs. Setting $d/dt = 0$ in equations (6.24),

(6.25), (6.30) and (6.31) we find that

$$\pi_y^{0*} = \frac{\sigma}{\mu+\eta}\pi_{h_1}^{0*}, \qquad \pi_z^{0*} = \frac{\sigma\alpha}{\mu+\eta}\pi_{h_2}^{0*}, \tag{6.44}$$
$$\pi_y^{1*} = \frac{(\eta\pi_y^{0*} + \sigma\pi_{h_1}^{1*})}{\mu}, \qquad \pi_z^{1*} = \frac{(\eta\pi_z^{0*} + \sigma\alpha\pi_{h_2}^{1*})}{\mu}.$$

Using equations (6.22) and (6.23), which are the main driving force for disease amongst naive IDUs, with $d/dt = 0$ we obtain

$$\pi_{h_1}^{0*} = A(1-\delta)\bigg(\lambda_0 s_{00}(1-\phi)\frac{\psi_0^*}{\pi^{0*}}\bigg(\alpha_h(\pi_{h_1}^{0*}+\pi_{h_2}^{0*}) + \alpha_y\pi_y^{0*}\bigg) + \lambda_0 s_{01}(1-\phi)\frac{\psi_1^*}{\pi^{1*}}\bigg(\alpha_h(\pi_{h_1}^{1*}+\pi_{h_2}^{1*}) + \alpha_y\pi_y^{1*}\bigg)\bigg),$$
$$\pi_{h_2}^{0*} = A\delta\bigg(\lambda_0 s_{00}(1-\phi)\frac{\psi_0^*}{\pi^{0*}}\bigg(\alpha_h(\pi_{h_1}^{0*}+\pi_{h_2}^{0*}) + \alpha_y\pi_y^{0*}\bigg) + \lambda_0 s_{01}(1-\phi)\frac{\psi_1^*}{\pi^{1*}}\bigg(\alpha_h(\pi_{h_1}^{1*}+\pi_{h_2}^{1*}) + \alpha_y\pi_y^{1*}\bigg)\bigg),$$

where $A = \dfrac{(\pi^{0*} - \pi_{h_1}^{0*} - \pi_{h_2}^{0*} - \pi_y^{0*} - \pi_z^{0*})}{(\mu+\sigma+\eta)}$. Adding these together gives

$$\pi_h^{0^*} = \frac{(\pi^{0*} - \pi_h^{0*} - \pi_y^{0*} - \pi_z^{0*})}{(\mu+\sigma+\eta)}\bigg(\lambda_0 s_{00}(1-\phi)\frac{\psi_0^*}{\pi^{0*}}\bigg(\alpha_h\pi_h^{0*} + \alpha_y\pi_y^{0*}\bigg) + \lambda_0 s_{01}(1-\phi)\frac{\psi_1^*}{\pi^{1*}}\bigg(\alpha_h\pi_h^{1*} + \alpha_y\pi_y^{1*}\bigg)\bigg),$$

where $\pi_h^{0*} = \pi_{h_1}^{0*} + \pi_{h_2}^{0*}$ and $\pi_h^{1*} = \pi_{h_1}^{1*} + \pi_{h_2}^{1*}$. Using the expressions (6.44) where necessary and noting that $\pi_{h_1}^{0*} = (1-\delta)\pi_h^{0*}$, which implies that $\pi_{h_2}^{0*} = \delta\pi_h^{0*}$ gives

$$\pi_h^{0*} = \frac{K_0^*}{(\mu+\sigma+\eta)}\bigg(1 - \frac{\pi_h^{0*}}{\pi^{0*}}\bigg(1 + \frac{\sigma(1-\delta)}{\mu+\eta} + \frac{\sigma\alpha\delta}{\mu+\eta}\bigg)\bigg), \tag{6.45}$$

where $K_0^* = \lambda_0 s_{00}(1-\phi)\psi_0^*(\alpha_h\pi_h^{0*} + \alpha_y\pi_y^{0*}) + \lambda_0 s_{01}(1-\phi)\frac{\psi_1^*\pi^{0*}}{\pi^{1*}}(\alpha_h\pi_h^{1*} + \alpha_y\pi_y^{1*})$. Consider the behaviour of the naive population over time, which is described by the following differential equation

$$\frac{d\pi^0}{dt} = \mu - (\mu+\eta)\pi^0. \tag{6.46}$$

This implies that

$$\pi^{0*} = \frac{\mu}{\mu+\eta}. \tag{6.47}$$

Solving (6.45) for π_h^{0*} and substituting in the equilibrium expression for π^{0*} gives

$$\pi_h^{0*} = \frac{\frac{K_0^*}{\mu+\sigma+\eta}}{1+\frac{K_0^*}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu}+\frac{\sigma(1-\delta)}{\mu}+\frac{\sigma\alpha\delta}{\mu}\right)}. \tag{6.48}$$

We now perform a similar procedure for the equations that drive HCV spread amongst experienced IDUs. Note that equations (6.28) and (6.29) imply that $\pi_{h_1}^{1*} = (1-\delta)\pi_h^{1*}$, and $\pi_{h_2}^{1*} = \delta\pi_h^{1*}$. Taking equations (6.28)-(6.29), adding them together with $d/dt = 0$ and substituting in the necessary equilibrium expressions (6.44) gives

$$\begin{aligned}\pi_h^{1*} = \frac{\eta\pi_h^{0*}}{\mu+\sigma} + \frac{K_1^*}{\mu+\sigma}\Bigg(1 - \frac{\pi_h^{1*}}{\pi^{1*}}\left[1+\frac{\sigma(1-\delta)}{\mu}+\frac{\sigma\alpha\delta}{\mu}\right] \\ - \frac{\eta\pi_h^{0*}}{\mu\pi^{1*}}\left[\frac{\sigma(1-\delta)}{\mu+\eta}+\frac{\sigma\alpha\delta}{\mu+\eta}\right]\Bigg),\end{aligned} \tag{6.49}$$

where $K_1^* = \lambda_1 s_{10}(1-\phi)\frac{\psi_0^*\pi^{1*}}{\pi^{0*}}(\alpha_h\pi_h^{0*}+\alpha_y\pi_y^{0*}) + \lambda_1 s_{11}(1-\phi)\psi_1^*(\alpha_h\pi_h^{1*}+\alpha_y\pi_y^{1*})$. Since $\pi^{0*}+\pi^{1*}=1$ and $\pi^{0*} = \mu/(\mu+\eta)$, then $\pi^{1*} = \eta/(\mu+\eta)$. Substituting this expression for π^{1*} and (6.48) into (6.49) gives

$$\pi_h^{1*} = \frac{\frac{\eta}{\mu+\sigma}\frac{K_0^*}{\mu+\sigma+\eta} + \frac{K_1^*}{\mu+\sigma}\left[1+\frac{K_0^*}{\mu+\sigma+\eta}\frac{\mu+\eta}{\mu}\right]}{\left[1+\frac{K_0^*}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu}+\frac{\sigma(1-\delta)}{\mu}+\frac{\sigma\alpha\delta}{\mu}\right)\right]\left[1+\frac{K_1^*}{\mu+\sigma}\frac{\mu+\eta}{\eta}\left(1+\frac{\sigma(1-\delta)}{\mu}+\frac{\sigma\alpha\delta}{\mu}\right)\right]}. \tag{6.50}$$

If we define $\boldsymbol{K} = (K_0, K_1)$ then using equilibrium expressions (6.44) along with expressions (6.48) and (6.50) it is possible to obtain a pair of algebraic non-linear equations for K_0, K_1 in matrix form

$$\boldsymbol{K} = \mathbf{M}(\boldsymbol{K})\boldsymbol{K}, \tag{6.51}$$

where $\mathbf{M}(\boldsymbol{K})$ is a positive strictly monotone decreasing function of $\boldsymbol{K}$ with

$M_{ij}(\boldsymbol{K}) = M_{ij}(K_0, K_1) \geq 0$ and $\mathbf{M}(\boldsymbol{0})^T$ gives the next generation matrix (6.42) (see Appendix A.4 for details).

We now turn our attention to what happens when $0 \leq R_0 \leq 1$. In this case we will show that when R_0 takes these values HCV will die out in all IDUs.

Lemma 6.1. *Suppose that $R_0 \leq 1$. Then the only non-negative solution $\boldsymbol{K}$ to $\boldsymbol{K}$=$\mathbf{M}(\boldsymbol{K})\boldsymbol{K}$ is $\boldsymbol{K}$=$\boldsymbol{0}$.*

Proof. If $\boldsymbol{K}$ is a strictly non-zero solution of (6.51) then

$$\boldsymbol{K} = \mathbf{M}(\boldsymbol{K})\boldsymbol{K} < \mathbf{M}(\boldsymbol{0})\boldsymbol{K}. \tag{6.52}$$

Since we have a strict inequality and $\boldsymbol{K}$ is a positive vector in (6.52) there exists an $\epsilon > 0$ with

$$\boldsymbol{K}(1+\epsilon) < \mathbf{M}(\boldsymbol{0})\boldsymbol{K}.$$

Multiplying both sides by $\mathbf{M}(\boldsymbol{0})$ gives

$$\mathbf{M}(\boldsymbol{0})\boldsymbol{K}(1+\epsilon) < \mathbf{M}^2(\boldsymbol{0})\boldsymbol{K}.$$

This implies that

$$\boldsymbol{K}(1+\epsilon)^2 < \mathbf{M}^2(\boldsymbol{0})\boldsymbol{K}. \tag{6.53}$$

Iterating gives

$$\boldsymbol{K}(1+\epsilon)^n < \mathbf{M}^n(\boldsymbol{0})\boldsymbol{K}. \tag{6.54}$$

Taking norms we have

$$|\boldsymbol{K}|(1+\epsilon)^n < |\mathbf{M}^n(\boldsymbol{0})\boldsymbol{K}| \leq ||\mathbf{M}^n(\boldsymbol{0})||\ |\boldsymbol{K}|.$$

This implies that

$$(1+\epsilon)^n < ||\mathbf{M}^n(\boldsymbol{0})||, \quad \text{(since } |\boldsymbol{K}| > 0\text{)},$$

which in turn gives

$$(1+\epsilon) < ||\mathbf{M}^n(\boldsymbol{0})||^{\frac{1}{n}}. \tag{6.55}$$

Since the spectral radius, ρ, of a matrix $\mathbf{M}$ is given by $\lim_{t\to\infty} ||\mathbf{M}^n||^{\frac{1}{n}}$ (Diekmann and Heesterbeek 2000), we let $n \to \infty$ in (6.55) to obtain

$$\rho(\mathbf{M}(\boldsymbol{0})) \geq 1+\epsilon,$$

where $\rho(\mathbf{M}(\boldsymbol{0}))$ denotes the spectral radius of the matrix $\mathbf{M}(\boldsymbol{0})$. Since the spectral radius of $\mathbf{M}(\boldsymbol{0})$ is equal to the basic reproductive number R_0, the statement above implies that $R_0 \geq 1+\epsilon$. This is a contradiction and so $|\boldsymbol{K}| = \boldsymbol{0}$ which implies that $\boldsymbol{K}=\boldsymbol{0}$. □

We are now going to examine what happens when $R_0 > 1$. We will now show that when $R_0 > 1$ there is an positive equilibrium which corresponds to a feasible equilibrium value for the model.

Theorem 6.1. *Suppose that $R_0 > 1$. Then the system given by (6.51) has at least one positive non-zero solution corresponding to a feasible equilibrium.*

Let C denote the cone of positive vectors:

$$C = \{(K_0, K_1) : K_0 \geq 0, K_1 \geq 0\}.$$

This is clearly a cone since multiplying K_0, K_1 or $\boldsymbol{K}$ by a scalar $\xi > 0$ results in a vector belonging to C. We use Theorem 1.6 of Gatica and Smith (1977) applied to the operator $T : C \to C$ given by $T(\boldsymbol{K}) = \mathbf{M}(\boldsymbol{K})\boldsymbol{K}$, which is given below.

Theorem 6.2. *Let $T : C \to C$ be a compact continuous operator acting on a Banach space, such that $T(\boldsymbol{0}) = \boldsymbol{0}$ and T is Fréchet differentiable at $\boldsymbol{K}=\boldsymbol{0}$ in the direction of the cone. Assume that T satisfies*

(a) $T'(\boldsymbol{0})$, the Fréchet derivative of T at $\boldsymbol{K}=\boldsymbol{0}$, has an eigenvector $\boldsymbol{k} \in C$ 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 $|\boldsymbol{x}_0| = R$.

In order to apply this theorem we need to show that

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

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

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

Lemma 6.2. *$T(\boldsymbol{K})$ is continuous in $\boldsymbol{K}$ for all $\boldsymbol{K} \geq \boldsymbol{0}$.*

Proof. Given $\epsilon > 0$, there exists $\delta > 0$ such that $|\boldsymbol{K} - \tilde{\boldsymbol{K}}| < \delta$ implies that

$$\max\{|M_{00}K_0 - \tilde{M}_{00}\tilde{K}_0|,\ |M_{01}K_1 - \tilde{M}_{01}\tilde{K}_1|,\ |M_{10}K_0 - \tilde{M}_{10}\tilde{K}_0|, \\ |M_{11}K_1 - \tilde{M}_{11}\tilde{K}_1|\} < \frac{\epsilon}{2\sqrt{2}}.$$

Hence for $|\boldsymbol{K} - \tilde{\boldsymbol{K}}| < \delta$

$$\begin{aligned} |M_{00}K_0 + M_{01}K_1 - \tilde{M}_{00}\tilde{K}_0 - \tilde{M}_{01}\tilde{K}_1| &\leq |M_{00}K_0 - \tilde{M}_{00}\tilde{K}_0| + |M_{01}K_1 - \tilde{M}_{01}\tilde{K}_1|, \\ &< \frac{\epsilon}{2\sqrt{2}} + \frac{\epsilon}{2\sqrt{2}}, \\ &= \frac{\epsilon}{\sqrt{2}}. \end{aligned}$$

Similarly

$$|M_{10}K_0 + M_{11}K_1 - \tilde{M}_{10}\tilde{K}_0 - \tilde{M}_{11}\tilde{K}_1| < \frac{\epsilon}{\sqrt{2}}.$$

Hence for $|\boldsymbol{K} - \tilde{\boldsymbol{K}}| < \delta$,

$$|T(\boldsymbol{K}) - T(\tilde{\boldsymbol{K}})| = |\mathbf{M}(\boldsymbol{K})\boldsymbol{K} - \mathbf{M}(\tilde{\boldsymbol{K}})\tilde{\boldsymbol{K}}|,$$

$$
\begin{aligned}
&= \sqrt{(B_0)^2 + (B_1)^2}, \\
&< \sqrt{\left(\frac{\epsilon}{\sqrt{2}}\right)^2 + \left(\frac{\epsilon}{\sqrt{2}}\right)^2}, \\
&= \epsilon,
\end{aligned}
$$

where $B_0 = M_{00}K_0 + M_{01}K_1 - \tilde{M}_{00}\tilde{K}_0 - \tilde{M}_{01}\tilde{K}_1$ and $B_1 = M_{10}K_0 + M_{11}K_1 - \tilde{M}_{10}\tilde{K}_0 - \tilde{M}_{11}\tilde{K}_1$. Hence $\mathrm{T}(\boldsymbol{K})$ is continuous in $\boldsymbol{K}$ for all $\boldsymbol{K} \geq \boldsymbol{0}$. □

Note that a function is bounded if its range is a bounded set (Kreyszig 1989).

Lemma 6.3. *T($\boldsymbol{K}$): $C \to C$ is bounded.*

Proof. We need to show that each of $M_{00}K_0 + M_{01}K_1$ and $M_{10}K_0 + M_{11}K_1$ is bounded in C. It is sufficient to show that each of $M_{00}K_0$, $M_{01}K_1$, $M_{10}K_0$ and $M_{11}K_1$ are bounded in C. It is obvious that each of these quantities is bounded below by 0. We now consider the upper bound. The term $M_{00}K_0$ is given by

$$
\left[\frac{\left(\lambda_0 s_{00}(1-\phi)\psi_0^*\left(\alpha_h + \frac{\sigma(1-\delta)}{\mu+\eta}\alpha_y\right) + \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\right)\frac{1}{\mu+\sigma+\eta}}{1 + \frac{K_0}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)} \right.
$$

$$
\left. + \frac{\lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}}\left(\alpha_h + \frac{\sigma(1-\delta)}{\mu}\alpha_y\right)\frac{\eta}{\mu+\sigma}\frac{1}{\mu+\sigma+\eta}}{\left[1 + \frac{K_0}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)\right]\left[1 + \frac{K_1}{\mu+\sigma}\frac{\mu+\eta}{\eta}\left(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)\right]} \right] K_0.
$$

We know that all of our parameters are fixed and finite so we can re-write the square bracketed term to obtain

$$
M_{00}K_0 = K_0\left[\frac{A_1}{1 + BK_0} + \frac{A_2}{(1 + BK_0)(1 + C_1K_1)}\right],
$$

where A_1, A_2, B and C_1 are constants independent of K_0 and K_1. Since $\frac{K_0}{1+BK_0} \leq \frac{1}{B}$ and $\frac{1}{1+C_1K_1} \leq 1$ we have

$$M_{00}K_0 \leq \frac{A_1}{B} + \frac{A_2}{B}.$$

Hence whatever K_0 and K_1, $M_{00}K_0$ is bounded in C.

We can perform a similar analysis to show that $M_{10}K_0$ is also bounded in C. If we examine $M_{10}K_0$ we see that it can be written in the following way:

$$\begin{aligned} M_{10}K_0 &= K_0\left[\frac{A_3}{1+BK_0} + \frac{A_4}{(1+BK_0)(1+C_1K_1)}\right], \\ &\leq \frac{A_3}{B} + \frac{A_4}{B}. \end{aligned}$$

Hence whatever K_0 and K_1, $M_{10}K_0$ is bounded in C.

We now turn our attention to the $M_{01}K_1$ and $M_{11}K_1$ terms. We know the $M_{01}K_1$ term is given by

$$K_1\left[\frac{\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\left(\alpha_h + \frac{\sigma(1-\delta)}{\mu}\alpha_y\right)\frac{1}{\mu+\sigma}\left(1+\frac{K_0}{\mu+\sigma+\eta}\frac{\mu+\eta}{\eta}\right)}{\left[1+\frac{K_0}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu}+\frac{\sigma(1-\delta)}{\mu}+\frac{\sigma\alpha\delta}{\mu}\right)\right]\left[1+\frac{K_1}{\mu+\sigma}\frac{\mu+\eta}{\eta}\left(1+\frac{\sigma(1-\delta)}{\mu}+\frac{\sigma\alpha\delta}{\mu}\right)\right]}\right].$$

Using a similar procedure to that used in our earlier calculations we obtain the following:

$$M_{01}K_1 = \frac{D_1K_1[1+D_2K_0]}{(1+BK_0)(1+C_1K_1)},$$

since $\frac{K_1}{1+K_1C_1} \leq \frac{1}{C_1}$ and $\frac{1+D_2K_0}{1+BK_0} \leq \frac{B+D_2}{B}$ we have

$$M_{01}K_1 \leq \frac{D_1}{C_1}\frac{B+D_2}{B}.$$

Hence whatever K_0 and K_1, $M_{01}K_1$ is bounded in C. Similarly

$$\begin{aligned} M_{11}K_1 &= \frac{D_3K_1[1+D_2K_0]}{(1+BK_0)(1+C_1K_1)}, \\ &\leq \frac{D_3}{C_1}\frac{B+D_2}{B}, \end{aligned}$$

which is also bounded in C whatever the values of K_0 and K_1. Hence $T(\boldsymbol{K})$: $C \rightarrow C$ given by $T(\boldsymbol{K}) = \mathbf{M}(\boldsymbol{K})\boldsymbol{K}$ is a bounded continuous operator in C, which is contained in a finite dimensional vector space. In a finite dimensional space every bounded operator with finite dimensional range is compact (Oden and Demkowicz 1996). Hence $T(\boldsymbol{K})$ is a continuous compact operator. □

We now wish to show that the operator $T(\boldsymbol{K})$ is Fréchet differentiable at $\boldsymbol{K}=\boldsymbol{0}$ in the direction of the cone C. The operator $T(\boldsymbol{K})$ is Fréchet differentiable at $\boldsymbol{K} = \boldsymbol{0}$ in the direction of the cone C if there is a bounded linear operator $T'(\boldsymbol{0})$ such that

$$T(\boldsymbol{K}) = T(\boldsymbol{0}) + T'(\boldsymbol{0})(\boldsymbol{K}) + o(|\boldsymbol{K}|)$$

for all $\boldsymbol{K}$ in C (Greenhalgh 1993). $T'(\boldsymbol{0})$ is called the Fréchet derivative of $T(\boldsymbol{K})$ at $\boldsymbol{K} = \boldsymbol{0}$ in the direction of the cone C. Note that a bounded linear operator is an operator that maps every bounded set into a bounded set (Kreyszig 1989).

Lemma 6.4. *$T(\boldsymbol{K})$ is Fréchet differentiable at $\boldsymbol{K}=\boldsymbol{0}$ in the direction of the cone C, with Fréchet derivative*

$$T'(\boldsymbol{0}) = \begin{bmatrix} M_{00}(\boldsymbol{0}) & M_{01}(\boldsymbol{0}) \\ M_{10}(\boldsymbol{0}) & M_{11}(\boldsymbol{0}) \end{bmatrix}$$

Proof. Clearly $T'(\boldsymbol{0})$ is a bounded linear operator. Define $\omega(\boldsymbol{K}) = T(\boldsymbol{K}) - T(\boldsymbol{0}) - T'(\boldsymbol{0})(\boldsymbol{K})$. If T is Fréchet differentiable in the direction of the cone C we

must show that $\omega(\boldsymbol{K}) = o(|\boldsymbol{K}|)$, for all $\boldsymbol{K} \in C$.

$$\begin{aligned}\omega(\boldsymbol{K}) &= \mathbf{M}(\boldsymbol{K})\boldsymbol{K} - \begin{bmatrix} M_{00}(\boldsymbol{0}) & M_{01}(\boldsymbol{0}) \\ M_{10}(\boldsymbol{0}) & M_{11}(\boldsymbol{0}) \end{bmatrix} \begin{bmatrix} K_0 \\ K_1 \end{bmatrix}, \\ &= \begin{bmatrix} (M_{00}(\boldsymbol{K}) - M_{00}(\boldsymbol{0}))K_0 + (M_{01}(\boldsymbol{K}) - M_{01}(\boldsymbol{0}))K_1 \\ (M_{10}(\boldsymbol{K}) - M_{10}(\boldsymbol{0}))K_0 + (M_{11}(\boldsymbol{K}) - M_{11}(\boldsymbol{0}))K_1 \end{bmatrix}.\end{aligned}$$

So

$$\begin{aligned}|\omega(\boldsymbol{K})| &\leq |(M_{00}(\boldsymbol{K}) - M_{00}(\boldsymbol{0}))K_0 + (M_{01}(\boldsymbol{K}) - M_{01}(\boldsymbol{0}))K_1| \\ &\quad + |(M_{10}(\boldsymbol{K}) - M_{10}(\boldsymbol{0}))K_0 + (M_{11}(\boldsymbol{K}) - M_{11}(\boldsymbol{0}))K_1|.\end{aligned}$$

Hence, using triangle inequalities we find that

$$\begin{aligned}\frac{|\omega(\boldsymbol{K})|}{|\boldsymbol{K}|} &\leq \Big|M_{00}(\boldsymbol{K}) - M_{00}(\boldsymbol{0})\Big|\frac{|K_0|}{|\boldsymbol{K}|} + \Big|M_{01}(\boldsymbol{K}) - M_{01}(\boldsymbol{0})\Big|\frac{|K_1|}{|\boldsymbol{K}|} \\ &\quad + \Big|M_{10}(\boldsymbol{K}) - M_{10}(\boldsymbol{0})\Big|\frac{|K_0|}{|\boldsymbol{K}|} + \Big|M_{11}(\boldsymbol{K}) - M_{11}(\boldsymbol{0})\Big|\frac{|K_1|}{|\boldsymbol{K}|}, \\ &\leq \sum_{i=0}^{1}\sum_{j=0}^{1}\big|M_{ij}(\boldsymbol{K}) - M_{ij}(\boldsymbol{0})\big|.\end{aligned}$$

Since the M_{ij} terms are continuous at $\boldsymbol{K} = \boldsymbol{0}$, given $\epsilon > 0$ there exists $\delta > 0$ such that $|\boldsymbol{K}| < \delta$ implies that $|M_{ij}(\boldsymbol{K}) - M_{ij}(\boldsymbol{0})| < \epsilon/4$ for $i, j = 0, 1$. Therefore

$$\begin{aligned}\frac{|\omega(\boldsymbol{K})|}{|\boldsymbol{K}|} &< 4\frac{\epsilon}{4}, \\ &= \epsilon.\end{aligned}$$

As $\epsilon > 0$ is arbitrary we deduce that $\omega(\boldsymbol{K}) = o(|\boldsymbol{K}|)$ and $T(\boldsymbol{K})$ is Fréchet differentiable at $\boldsymbol{K}=\boldsymbol{0}$ in the direction of the cone C, with Fréchet derivative

$$T'(\boldsymbol{0}) = \begin{bmatrix} M_{00}(\boldsymbol{0}) & M_{01}(\boldsymbol{0}) \\ M_{10}(\boldsymbol{0}) & M_{11}(\boldsymbol{0}) \end{bmatrix}.$$

□

We are now going to show that $T'(\boldsymbol{0})$ has an eigenvector corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C. It is straightforward to show that the Fréchet derivative of T at $\boldsymbol{K} = \boldsymbol{0}$ is given by the transpose of the next generation matrix (6.42) (see Appendix A.4).

Since $T'(\boldsymbol{0})$ is a matrix with positive entries we can use the Perron-Frobenius theory of positive matrices (Meyer 2000) which tells us that there is a positive real number r such that r is an eigenvalue of $T'(\boldsymbol{0})$ and any other eigenvalue is strictly smaller in absolute value. The spectral radius of $T'(\boldsymbol{0})$, $\rho(T'(\boldsymbol{0})) = r$ and furthermore there is an eigenvector with strictly positive entries corresponding to the eigenvalue r.

Hence if $\rho(T'(\boldsymbol{0})) > 1$, $T'(\boldsymbol{0})$ has an eigenvector $\boldsymbol{v} \in C$ which corresponds to an eigenvalue $\omega_0 > 1$. The theory also states that there are no other positive eigenvectors. Hence 1 cannot be an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C and the lemma below follows.

Lemma 6.5. *If $R_0 > 1$, $T'(\boldsymbol{0})$ has an eigenvector $\boldsymbol{v} \in C$ corresponding to an eigenvalue $\omega_0 > 1$ and 1 is not an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C.*

We now prove condition (c) of the conditions immediately following Theorem 6.2.

Lemma 6.6. *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. Let $\boldsymbol{x} \in C$ with $|\boldsymbol{x}| = R$ and $T(\boldsymbol{x}) = \mu\boldsymbol{x}$. Since $T(\boldsymbol{x}) \geq \boldsymbol{0}\ \forall \boldsymbol{x} \geq \boldsymbol{0}$ then $\mu \geq 0$. Now let $\boldsymbol{y} \in C$ where $\boldsymbol{y} = \boldsymbol{x}/R$ and $|\boldsymbol{y}| = 1$. Then

$$\mu\boldsymbol{x} = T(\boldsymbol{x}).$$

This implies that

$$\mu R\boldsymbol{y} = T(R\boldsymbol{y}).$$

Dividing by R

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

Hence $|\mu \boldsymbol{y}| = \mu |\boldsymbol{y}| = \mu = \dfrac{1}{R}|T(R\boldsymbol{y})|$. Since $T(R\boldsymbol{y})$ is bounded above by a positive constant, c^* say (independent of R), we have

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

So if $R \geq c^*$ $\mu \leq 1$. □

This lemma completes the proof of the three conditions that are needed to apply Theorem 6.2 and we can conclude that when $R_0 > 1$ there exists a non-zero equilibrium $\boldsymbol{x}_0 \in C$.

We now need to show that such an equilibrium value corresponds to a feasible endemic equilibrium for the full model. If each of the equilibrium values $\pi_x^{0*}, \pi_{x_1}^{0*}, \pi_{h_1}^{0*}$ ... $\pi_{h_2}^{1*}, \pi_y^{1*}$ and π_z^{1*} is positive then the endemic equilibrium value is feasible.

Setting $d/dt = 0$ in equation (6.20) we obtain

$$0 = \mu - (\mu + \eta)\pi_x^{0*} - \pi_x^{0*}\frac{K_0^*}{\pi^{0*}},$$

this implies that

$$\pi_x^{0*} = \frac{\mu}{\mu + \eta + \frac{K_0^*}{\pi^{0*}}}, \tag{6.56}$$

where $K_0^* = \lambda_0 s_{00}(1-\phi)\psi_0^*(\alpha_h \pi_h^{0*} + \alpha_y \pi_y^{0*}) + \lambda_0 s_{01}(1-\phi)\frac{\psi_1^* \pi^{0*}}{\pi^{1*}}(\alpha_h \pi_h^{1*} + \alpha_y \pi_y^{1*})$. Using a similar method as above with equations (6.21), (6.24) and (6.25) and using the relationships $\pi_{h_1}^{0*} = (1-\delta)\pi_h^{0*}$ and $\pi_{h_2}^{0*} = \delta \pi_h^{0*}$ we obtain

$$\pi_{x_1}^{0*} = \frac{\sigma(1-\alpha)\delta \pi_h^{0*}}{\mu + \eta + \frac{K_0^*}{\pi^{0*}}}, \tag{6.57}$$

$$\pi_y^{0*} = \frac{\sigma(1-\delta)}{\mu + \eta}\pi_h^{0*}, \tag{6.58}$$

$$\pi_z^{0*} = \frac{\sigma\alpha\delta}{\mu + \eta}\pi_h^{0*}. \tag{6.59}$$

If $\boldsymbol{K}^* = \mathbf{M}(\boldsymbol{K}^*)\boldsymbol{K}^*$ corresponds to a non-zero equilibrium then it is clear that both $\boldsymbol{K}_0^*$ and $\boldsymbol{K}_1^*$ must be strictly positive. From equation (6.48) we deduce that π_h^{0*} is strictly positive. Therefore π_x^{0*}, $\pi_{x_1}^{0*}$, π_y^{0*} and π_z^{0*} given by equations (6.56)-(6.59) are all strictly greater than zero. Performing similar calculations with equations (6.26), (6.27), (6.30) and (6.31) and using the relationships $\pi_{h_1}^{1*} = (1-\delta)\pi_h^{1*}$ and $\pi_{h_2}^{1*} = \delta \pi_h^{1*}$ we obtain the following results:

$$\pi_x^{1*} = \frac{\eta \pi_x^{0*}}{\mu + \frac{K_1^*}{\pi^{1*}}}, \tag{6.60}$$

$$\pi_{x_1}^{1*} = \frac{\eta \pi_{x_1}^{0*} + \sigma(1-\alpha)\delta \pi_h^{1*}}{\mu + \frac{K_1^*}{\pi^{1*}}}, \tag{6.61}$$

$$\pi_y^{1*} = \frac{\eta \pi_y^{0*} + \sigma(1-\delta)\pi_h^{1*}}{\mu}, \tag{6.62}$$

$$\pi_z^{1*} = \frac{\eta \pi_z^{0*} + \sigma\alpha\delta \pi_h^{1*}}{\mu}, \tag{6.63}$$

where $K_1^* = \lambda_1 s_{10}(1-\phi)\frac{\psi_{0^*}\pi^{1^*}}{\pi^{0*}}(\alpha_h \pi_h^{0*} + \alpha_y \pi_y^{0*}) + \lambda_1 s_{11}(1-\phi)\psi_{1^*}(\alpha_h \pi_h^{1*} + \alpha_y \pi_y^{1*})$. We know that $K_1^* > 0$ and from equation (6.50) $\pi_h^{1^*} > 0$. It follows that π_x^{1*}, $\pi_{x_1}^{1*}$, π_y^{1*} and π_z^{1*} given by equations (6.60)-(6.63) are all strictly positive. Moreover, adding the equilibrium versions of equations (6.20)-(6.31) we deduce that $\pi_x^{0*} + \pi_{x_1}^{0*} + \pi_{h_1}^{0*} + \pi_{h_2}^{0*} + \pi_y^{0*} + \pi_z^{0*} + \pi_x^{1*} + \pi_{x_1}^{1*} + \pi_{h_1}^{1*} + \pi_{h_2}^{1*} + \pi_y^{1*} + \pi_z^{1*} = 1$. Hence each non-zero equilibrium point of (K_0^*, K_1^*) corresponds to a feasible equilibrium value.

We are now going to prove that the endemic equilibrium solution to our model is unique. Lajmanovich and Yorke (1976) developed a deterministic model to

examine the spread of gonorrhea in an non-homogeneous population which they assume can be separated into n homogeneous groups (each member of the group has the same recovery rate and mixing patterns). This allowed the authors to examine the equilibria and stability of the system

$$\frac{d\boldsymbol{y}}{dt} = \boldsymbol{A}\boldsymbol{y} + \boldsymbol{N}(\boldsymbol{y}),$$

where $\boldsymbol{A} = (a_{ij})$ is a matrix with $a_{ij} = \beta_{ji}c_i$, $j \neq i$, $a_{ii} - \beta_{ii}c_i - \alpha_i$ and $\boldsymbol{N}(\boldsymbol{y}) = \sum_{j=1}^{n} \beta_{ji} y_j y_i$. Here, β_{ij} denotes the contact rate of the susceptibles of the ith group with the infecteds of the jth group, y_i denotes the number of infecteds in the ith group, α_i denotes the recovery rate and c_i denotes the size of the population. All parameters are strictly positive. During the course of their analysis the authors were able to prove a number of key results on the behaviour of the model. They showed that provided that disease was initially present in the population, no group can have all its individuals uninfected for a positive time period. Similarly, the authors showed that no group can have all its individuals infected for a positive time period. Equilibrium and stability analysis showed that there were two scenarios; one where the disease eventually died out in all groups and one where the disease remained endemic and the proportion of susceptibles and infecteds of each group tended to non-zero constant levels, independent of the initial conditions. In each case the equilibrium value was shown to be globally asymptotically stable. While our model does not quite fit into this framework it is quite similar and we can modify the techniques the authors use in their uniqueness proof to fit into our model.

We can think of the two quantities $\pi_h^0 = \pi_{h_1}^0 + \pi_{h_2}^0$ and $\pi_h^1 = \pi_{h_1}^1 + \pi_{h_2}^1$, respectively the number of naive and experienced IDUs in the acute phase (either h_1 or h_2) as driving the disease in our two class model. These satisfy the following equations:

$$\begin{aligned}\frac{d\pi_h^0}{dt} = &\left[\lambda_0(1-\phi)s_{00}\frac{\psi_0}{\pi^0}\left(\alpha_h\pi_h^0 + \alpha_y\pi_y^0\right) + \lambda_0(1-\phi)s_{01}\frac{\psi_1}{\pi^1}\left(\alpha_h\pi_h^1 + \alpha_y\pi_y^1\right)\right] \\ &\times (\pi^0 - \pi_h^0 - \pi_y^0 - \pi_z^0) - (\mu + \sigma + \eta)\pi_h^0,\end{aligned}$$

$$\frac{d\pi_h^1}{dt} = \left[\lambda_1(1-\phi)s_{10}\frac{\psi_0}{\pi^0}\big(\alpha_h\pi_h^0 + \alpha_y\pi_y^0\big) + \lambda_1(1-\phi)s_{11}\frac{\psi_1}{\pi^1}\big(\alpha_h\pi_h^1 + \alpha_y\pi_y^1\big)\right]$$
$$\times (\pi^1 - \pi_h^1 - \pi_y^1 - \pi_z^1) + \eta\pi_h^0 - (\mu+\sigma)\pi_h^1.$$

Setting $d/dt = 0$ in these equations and substituting in the necessary equilibrium values (6.44) with $\pi_{h_1}^{0*} = (1-\delta)\pi_h^{0*}$, $\pi_{h_1}^{1*} = (1-\delta)\pi_h^{1*}$, $\pi_{h_2}^{0*} = \delta\pi_h^{0*}$ and $\pi_{h_2}^{1*} = \delta\pi_h^{1*}$ we obtain

$$0 = \left[\lambda_0(1-\phi)s_{00}\psi_0^*\left(\alpha_h + \alpha_y\frac{\sigma(1-\delta)}{\mu+\eta}\right)\pi_h^{0*}\right.$$
$$\left. + \lambda_0(1-\phi)s_{01}\frac{\psi_1^*\pi^{0*}}{\pi^{1*}}\left[\left(\alpha_h + \alpha_y\frac{\sigma(1-\delta)}{\mu}\right)\pi_h^{1*} + \frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\pi_h^{0*}\right]\right]\times$$
$$\left(1 - \frac{\pi_h^{0*}}{\pi^{0*}}\left(1 + \frac{\sigma(1-\delta)}{\mu+\eta} + \frac{\sigma\alpha\delta}{\mu+\eta}\right)\right) - (\mu+\sigma+\eta)\pi_h^{0*},$$
$$0 = \eta\pi_h^{0^*} + \left[\lambda_1(1-\phi)s_{10}\frac{\psi_0^*\pi^{1*}}{\pi^{0*}}\left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu+\eta}\right)\pi_h^{0*}\right.$$
$$\left. + \lambda_1(1-\phi)s_{11}\psi_1^*\left[\left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right)\pi_h^{1*} + \frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\pi_h^{0*}\right]\right]\times$$
$$\left(1 - \frac{\pi_h^{1*}}{\pi^{1*}}\left(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right) - \frac{\pi_h^{0*}}{\pi^{1*}}\left(\frac{\eta\sigma(1-\delta)}{\mu(\mu+\eta)} + \frac{\eta\sigma\delta\alpha}{\mu(\mu+\eta)}\right)\right) - (\mu+\sigma)\pi_h^{1*}.$$

Note that ψ_0^* and ψ_1^* depend on the unique equilibrium values of m_0, m_1, n_0 and n_1, the number of needles and IDUs in the two groups but they do not depend on π_h^{0*} and π_h^{1*} or the other equilibrium proportions of IDUs in different disease stages and experience classes.

These equations are of the form

$$0 = (\beta_{11}\pi_h^{0*} + \beta_{12}\pi_h^{1*})(1 - c_1\pi_h^{0*}) - \alpha_1\pi_h^{0*}, \tag{6.64}$$
$$0 = \eta\pi_h^{0*} + (\beta_{21}\pi_h^{0*} + \beta_{22}\pi_h^{1*})(1 - c_2\pi_h^{0*} - c_3\pi_h^{1*}) - \alpha_2\pi_h^{1*}, \tag{6.65}$$

where $\beta_{ij} > 0$, $\alpha_i > 0$, $c_i > 0$, $i,j = 1,2$, $c_3 > 0$ and the terms $1 - c_1\pi_h^{0*}$ and $1 - c_2\pi_h^{0*} - c_3\pi_h^{1*}$ correspond to the terms

$$1 - \frac{1}{\pi^{0*}}(\pi_h^{0*} + \pi_y^{0*} + \pi_z^{0*})$$

and

$$1 - \frac{1}{\pi^{1*}}(\pi_h^{1*} + \pi_y^{1*} + \pi_z^{1*})$$

respectively. If a solution to this two dimensional system is feasible then the terms given by $1 - c_1\pi_h^{0*}$ and $1 - c_2\pi_h^{0*} - c_3\pi_h^{1*}$ cannot be negative. Hence, $1 \geq c_1\pi_h^{0*}$ and $1 \geq c_2\pi_h^{0*} + c_3\pi_h^{1*}$.

We now show that both $\pi_h^{0^*}$ and $\pi_h^{1^*}$ are strictly positive for a feasible endemic equilibrium value.

Lemma 6.7. *If (π_h^{0*}, π_h^{1*}) corresponds to a feasible equilibrium solution for the system (6.20)-(6.31) with $\pi_h^{0*} \geq 0$ and $\pi_h^{1*} \geq 0$ and $(\pi_h^{0*}, \pi_h^{1*}) \neq (0, 0)$ then $\pi_h^{0*} > 0$ and $\pi_h^{1*} > 0$.*

Proof. To prove this lemma we examine two separate cases:

Case 1. $\pi_h^{0*} = 0$.

Substituting $\pi_h^{0*} = 0$ into equation (6.64) we find that $\beta_{12}\pi_h^{1*} = 0$ which implies that $\pi_h^{1*} = 0$. Since π_h^{0*} and π_h^{1*} cannot both be zero we deduce that $\pi_h^{0*} > 0$.

Case 2. $\pi_h^{1*} = 0$.

Substituting $\pi_h^{1*} = 0$ into equation (6.65) we find that

$$\eta + \beta_{21}(1 - c_2\pi_h^{0*}) = 0. \tag{6.66}$$

Since (π_h^{0*}, π_h^{1*}) corresponds to a feasible equilibrium solution we have noted that $(1 - c_2\pi_h^{0*}) \geq 0$. This means that we have a contradiction to equation (6.66) and therefore $\pi_h^{1*} > 0$.

□

We will now show that the non-zero equilibrium solution of this two dimensional system is unique.

Lemma 6.8. *If $R_0 > 1$ then there is at most one non-zero equilibrium solution (π_h^{0*}, π_h^{1*}) corresponding to a feasible equilibrium.*

Proof. Suppose that (π_h^{0*}, π_h^{1*}) and $(\rho_h^{0*}, \rho_h^{1*})$ are two non-zero feasible equilibrium solutions to the two dimensional system. Since both (π_h^{0*}, π_h^{1*}) and $(\rho_h^{0*}, \rho_h^{1*})$ correspond to feasible equilibria we must have $1 - c_1\pi_h^{0*} \geq 0$, $1 - c_1\rho_h^{0*} \geq 0$, $1 - c_2\pi_h^{0*} - c_3\pi_h^{1*} \geq 0$ and $1 - c_2\rho_h^{0*} - c_3\rho_h^{1*} \geq 0$.

If $\pi_h^{0*} \neq \rho_h^{0*}$ then $\pi_h^{0*}/\rho_h^{0*} \neq 1$, so either $\pi_h^{0*}/\rho_h^{0*} < 1$ or $\pi_h^{0*}/\rho_h^{0*} > 1$. If $\pi_h^{0*}/\rho_h^{0*} < 1$ we can re-define our variables to allow us to assume without loss of generality that $\pi_h^{0*}/\rho_h^{0*} > 1$. Now we must have one of the two cases:

Case 1.

$$\frac{\pi_h^{0*}}{\rho_h^{0*}} \geq \frac{c_2\pi_h^{0*} + c_3\pi_h^{1*}}{c_2\rho_h^{0*} + c_3\rho_h^{1*}} \text{ and } \frac{\pi_h^{0*}}{\rho_h^{0*}} > 1,$$

which implies that

$$(c_2\rho_h^{0*} + c_3\rho_h^{1*})\pi_h^{0*} \geq (c_2\pi_h^{0*} + c_3\pi_h^{1*})\rho_h^{0*}.$$

From this we deduce that

$$\frac{\pi_h^{0*}}{\rho_h^{0*}} \geq \frac{\pi_h^{1*}}{\rho_h^{1*}}.$$

Case 2.

$$\frac{c_2\pi_h^{0*} + c_3\pi_h^{1*}}{c_2\rho_h^{0*} + c_3\rho_h^{1*}} \geq \frac{\pi_h^{0*}}{\rho_h^{0*}} > 1.$$

This implies that

$$\rho_h^{0*}(c_2\pi_h^{0*} + c_3\pi_h^{1*}) \geq \pi_h^{0*}(c_2\rho_h^{0*} + c_3\rho_h^{1*}).$$

From this we deduce that

$$\frac{\pi_h^{1*}}{\rho_h^{1*}} \geq \frac{\pi_h^{0*}}{\rho_h^{0*}}.$$

In Case 1

$$0 = (\beta_{11}\pi_h^{0*} + \beta_{12}\pi_h^{1*})(1 - c_1\pi_h^{0*}) - \alpha_1\pi_h^{0*}.$$

Multiplying both sides by $\frac{\rho_h^{0*}}{\pi_h^{0*}}$ we obtain

$$0 = \left(\beta_{11}\rho_h^{0*} + \beta_{12}\frac{\pi_h^{1*}\rho_h^{0*}}{\pi_h^{0*}}\right)(1 - c_1\pi_h^{0*}) - \alpha_1\rho_h^{0*}.$$

Since $\rho_h^{1*} \geq \frac{\pi_h^{1*}\rho_h^{0*}}{\pi_h^{0*}}$ and $\pi_h^{0*} > \rho_h^{0*}$ we find that

$$0 < (\beta_{11}\rho_h^{0*} + \beta_{12}\rho_h^{1*})(1 - c_1\rho_h^{0*}) - \alpha_1\rho_h^{0*}. \tag{6.67}$$

Since the right hand side of inequality (6.67) must equal zero we have a contradiction.

In Case 2

$$0 = \eta\pi_h^{0*} + (\beta_{21}\pi_h^{0*} + \beta_{22}\pi_h^{1*})(1 - c_2\pi_h^{0*} - c_3\pi_h^{1*}) - \alpha_2\pi_h^{1*},$$

Multiplying both sides by $\frac{\rho_h^{1*}}{\pi_h^{1*}}$ we obtain

$$0 = \frac{\eta\pi_h^{0*}\rho_h^{1*}}{\pi_h^{1*}} + \left(\beta_{21}\frac{\pi_h^{0*}\rho_h^{1*}}{\pi_h^{1*}} + \beta_{22}\rho_h^{1*}\right)(1 - c_2\pi_h^{0*} - c_3\pi_h^{1*}) - \alpha_2\rho_h^{1*}.$$

Since $\rho_h^{0*} \geq \frac{\pi_h^{0*}\rho_h^{1*}}{\pi_h^{1*}}$, $\pi_h^{0*} > \rho_h^{0*}$ and $\pi_h^{1*} > \rho_h^{1*}$ we find that

$$0 < \eta\rho_h^{0*} + (\beta_{21}\rho_h^{0*} + \beta_{22}\rho_h^{1*})(1 - c_2\rho_h^{0*} - c_3\rho_h^{1*}) - \alpha_2\rho_h^{1*}. \tag{6.68}$$

Since the right hand side of inequality (6.68) must equal zero we have another contradiction and hence there is at most one solution corresponding to a feasible non-zero equilibrium. □

6.6 Global stability

We are now going to examine the stability of the DFE when R_0 takes values between 0 and 1 inclusive.

Theorem 6.3. *When $R_0 \leq 1$ the DFE is globally asymptotically stable.*

Proof. This result is proved in several stages using a method similar to that used in the proof of Theorem 3.2. We write $\pi_h^{0,\infty}$ for $\limsup_{t\to\infty}\pi_h^0(t)$, where $\pi_h^0(t) = \pi_{h_1}^0(t) + \pi_{h_2}^0(t)$. Similar definitions are used for $\pi_y^{0,\infty}$, $\pi_y^{1,\infty}$ and $\pi_h^{1,\infty}$, where $\pi_h^1(t) = \pi_{h_1}^1(t) + \pi_{h_2}^1(t)$. We first prove several results that give upper bounds on the limit suprema of $\pi_y^{0,\infty}$, $\pi_y^{1,\infty}$, $\pi_h^{0,\infty}$ and $\pi_h^{1,\infty}$. Using equations (6.22), (6.23), (6.28) and (6.29) we are able to find relationships between $\pi_{h_1}^{0,\infty}$ and $\pi_{h_2}^{0,\infty}$ as well as $\pi_{h_1}^{1,\infty}$ and $\pi_{h_2}^{1,\infty}$, thus allowing us to express our earlier results in terms of two limit suprema. We then show if $R_0 \leq 1$ these limit suprema must be equal to zero. The global stability of the DFE then follows.

Lemma 6.9. $\pi_h^{0,\infty} \leq \dfrac{\overline{K}_0}{\mu+\sigma+\eta+\frac{\overline{K}_0}{\pi^{0*}}}$,

where $\overline{K}_0 = \lambda_0 s_{00}(1-\phi)\psi_0^*(\alpha_h\pi_h^{0,\infty}+\alpha_y\pi_y^{0,\infty})+\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\mu}{\eta}(\alpha_h\pi_h^{1,\infty}+\alpha_y\pi_y^{1,\infty})$.

Proof. Taking equations (6.22) and (6.23) together we have

$$\begin{aligned}
\frac{d\pi_h^0}{dt} &= \left[\lambda_0 s_{00}(1-\phi)\frac{\psi_0}{\pi^0}(\alpha_h\pi_h^0+\alpha_y\pi_y^0)+\lambda_0 s_{01}(1-\phi)\frac{\psi_1}{\pi^1}(\alpha_h\pi_h^1+\alpha_y\pi_y^1)\right] \\
&\quad\times(\pi^0-\pi_h^0-\pi_y^0-\pi_z^0)-(\mu+\sigma+\eta)\pi_h^0, \\
&= \left[\lambda_0 s_{00}(1-\phi)\psi_0(\alpha_h\pi_h^0+\alpha_y\pi_y^0)+\lambda_0 s_{01}(1-\phi)\frac{\psi_1\pi^0}{\pi^1}(\alpha_h\pi_h^1+\alpha_y\pi_y^1)\right] \\
&\quad\times\left(1-\frac{1}{\pi^0}\left(\pi_h^0+\pi_y^0+\pi_z^0\right)\right)-(\mu+\sigma+\eta)\pi_h^0,
\end{aligned}$$

$$\leq \left[\lambda_0 s_{00}(1-\phi)\psi_0(\alpha_h\pi_h^0+\alpha_y\pi_y^0)+\lambda_0 s_{01}(1-\phi)\frac{\psi_1\pi^0}{\pi^1}(\alpha_h\pi_h^1+\alpha_y\pi_y^1)\right]$$
$$\times \left(1-\frac{\pi_h^0}{\pi^0}\right)-(\mu+\sigma+\eta)\pi_h^0.$$

Note that π^0 and π^1 depend on time but as $t\to\infty$ we know that $\pi^0\to\pi^{0*}=\mu/(\mu+\eta)$ and $\pi^1\to\pi^{1*}=\eta/(\mu+\eta)$. Also as $t\to\infty$ $\psi_0\to\psi_0^*$ and $\psi_1\to\psi_1^*$ (Appendix A.1). Hence given $\epsilon>0$ there exists $t_0>0$ such that for all $t\geq t_0$

$$\psi_0\leq\psi_0^*+\epsilon$$

and

$$\frac{\pi^0}{\pi^1}\psi_1\leq\frac{\mu}{\eta}\psi_1^*+\epsilon.$$

Hence

$$\frac{d\pi_h^0}{dt}\leq\left[\lambda_0 s_{00}(1-\phi)(\psi_0^*+\epsilon)(\alpha_h\pi_h^0+\alpha_y\pi_y^0)\right.$$
$$\left.+\lambda_0 s_{01}(1-\phi)\left(\frac{\mu}{\eta}\psi_1^*+\epsilon\right)(\alpha_h\pi_h^1+\alpha_y\pi_y^1)\right]\left(1-\frac{\pi_h^0}{\pi^0}\right)-(\mu+\sigma+\eta)\pi_h^0.$$

Given $\epsilon>0$ there exists $t_1>0$ such that for all $t\geq t_1$

$$\pi_h^0\leq\pi_h^{0,\infty}+\frac{\epsilon}{4\lambda_0 s_{00}(1-\phi)(\psi_0^*+\epsilon)\alpha_h},$$
$$\pi_y^0\leq\pi_y^{0,\infty}+\frac{\epsilon}{4\lambda_0 s_{00}(1-\phi)(\psi_0^*+\epsilon)\alpha_y},$$
$$\pi_h^1\leq\pi_h^{1,\infty}+\frac{\epsilon}{4\lambda_0 s_{01}(1-\phi)(\frac{\mu}{\eta}\psi_1^*+\epsilon)\alpha_h},$$
$$\pi_y^1\leq\pi_y^{1,\infty}+\frac{\epsilon}{4\lambda_0 s_{01}(1-\phi)(\frac{\mu}{\eta}\psi_1^*+\epsilon)\alpha_y}.$$

Hence for all $t\geq\max(t_0,t_1)$

$$\frac{d\pi_h^0}{dt}\leq\left(1-\frac{\pi_h^0}{\pi^0}\right)(\overline{K}_0+\epsilon)-(\mu+\sigma+\eta)\pi_h^0,$$

where $\overline{K}_0=\lambda_0 s_{00}(1-\phi)\psi_0^*(\alpha_h\pi_h^{0,\infty}+\alpha_y\pi_y^{0,\infty})+\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\mu}{\eta}(\alpha_h\pi_h^{1,\infty}+\alpha_y\pi_y^{1,\infty})$.

Again we note that $1/\pi^0 \to (\mu+\eta)/\mu$ as $t \to \infty$. Hence given $\epsilon_1 > 0$ there exists $t_2 > 0$ such that for all $t \geq t_2$

$$\frac{1}{\pi^0} \geq \frac{\mu+\eta}{\mu} - \epsilon_1.$$

Therefore for all $t \geq \bar{t}$, where $\bar{t} = \max(t_0, t_1, t_2)$

$$\begin{aligned}\frac{d\pi_h^0}{dt} &\leq \left(1 - \pi_h^0\left(\frac{\mu+\eta}{\mu} - \epsilon_1\right)\right)(\overline{K}_0 + \epsilon) - (\mu+\sigma+\eta)\pi_h^0, \\ &\leq (1+\epsilon_1)(\overline{K}_0+\epsilon) - \left(\mu+\sigma+\eta+\frac{(\overline{K}_0+\epsilon)}{\pi^{0*}}\right)\pi_h^0. \qquad (6.69)\end{aligned}$$

From equation (6.69) we have

$$\frac{d}{dt}\left[\pi_h^0 \exp(Wt)\right] \leq (1+\epsilon_1)(\overline{K}_0+\epsilon)\exp(Wt),$$

where $W = \mu+\sigma+\eta+\frac{(\overline{K}_0+\epsilon)}{\pi^{0*}}$. Integrating over $[\bar{t}, t]$ gives

$$\pi_h^0(t) \leq \frac{(\overline{K}_0+\epsilon)(1+\epsilon_1)}{W}\left[1 - \exp[(-W)(t-\bar{t})]\right] + \pi_h^0(\bar{t})\exp[(-W)(t-\bar{t})].$$

So given $\epsilon_2 > 0$ there exists $t_3 > 0$ such that

$$\pi_h^0(t) \leq \frac{(\overline{K}_0+\epsilon)(1+\epsilon_1)}{W} + \epsilon_2, \quad \forall t \geq t_3.$$

Taking the limsup and letting $t \to \infty$ we have

$$\pi_h^{0,\infty} \leq \frac{(\overline{K}_0+\epsilon)(1+\epsilon_1)}{\mu+\sigma+\eta+\frac{(\overline{K}_0+\epsilon)}{\pi^{0*}}} + \epsilon_2.$$

Since ϵ, ϵ_1, $\epsilon_2 > 0$ are arbitrary, letting these all tend to zero the result follows. □

Similarly, we have the following result:

Lemma 6.10. $\pi_h^{1,\infty} \leq \dfrac{\overline{K}_1 + \eta\pi_h^{0,\infty}}{\mu+\sigma+\frac{\overline{K}_1}{\pi^{1*}}}$,

where $\overline{K}_1 = \lambda_1 s_{10}(1-\phi)\psi_0^* \frac{\eta}{\mu}(\alpha_h \pi_h^{0,\infty} + \alpha_y \pi_y^{0,\infty}) + \lambda_1 s_{11}(1-\phi)\psi_1^*(\alpha_h \pi_h^{1,\infty} + \alpha_y \pi_y^{1,\infty})$.

Proof. Using equations (6.28) and (6.29) along with the method used in the proof of Lemma 6.9 the result follows. □

We are now going to use the same techniques used to prove Lemma 3.1 to prove results that give upper bounds on the limit suprema of π_y^0 and π_y^1 in terms of $\pi_{h_1}^{0,\infty}$ and $\pi_{h_1}^{1,\infty}$.

Lemma 6.11. $\pi_y^{0,\infty} \leq \dfrac{\sigma \pi_{h_1}^{0,\infty}}{\mu + \eta}$.

Proof. Given $\epsilon > 0$ from equation (6.24) we have, noting that $\pi_{h_1}^0 \leq \pi_{h_1}^{0,\infty} + \epsilon$, $\forall t \geq t_4(\epsilon)$

$$\frac{d}{dt}\left[\pi_y^0 \exp((\mu+\eta)t)\right] \leq (\pi_{h_1}^{0,\infty} + \epsilon)\sigma \exp((\mu+\eta)t), \quad \forall t \geq t_4(\epsilon),\ \epsilon > 0.$$

Integrating over $[t_4(\epsilon), t]$ gives

$$\pi_y^0(t) \leq \epsilon + \frac{(\pi_{h_1}^{0,\infty} + \epsilon)\sigma}{\mu + \eta} \quad \forall t \geq t_5(\epsilon), \text{ for some } t_5(\epsilon) > t_4(\epsilon) \text{ sufficiently large.}$$

Taking the limsup and letting $t \to \infty$ we have

$$\pi_y^{0,\infty} \leq \frac{\pi_{h_1}^{0,\infty}\sigma}{\mu + \eta} + \epsilon_1, \qquad \text{where } \epsilon_1 = \epsilon\left(\frac{\mu + \sigma + \eta}{\mu + \eta}\right).$$

Since $\epsilon_1 > 0$ is arbitrary, the result follows. □

Lemma 6.12. $\pi_y^{1,\infty} \leq \dfrac{\sigma \pi_{h_1}^{1,\infty}}{\mu} + \dfrac{\eta\sigma\pi_{h_1}^{0,\infty}}{\mu(\mu+\eta)}$

Proof. Using equation (6.30) along with the method used in the proof of Lemma 6.11 the result follows. □

We now use equations (6.22) and (6.23) to find a relationship between $\pi_{h_1}^{0,\infty}$ and $\pi_{h_2}^{0,\infty}$.

Lemma 6.13. $(1-\delta)\pi_{h_2}^{0,\infty} = \delta\pi_{h_1}^{0,\infty}$.

Proof. We begin by proving that $\delta\pi_{h_1}^{0,\infty} \leq (1-\delta)\pi_{h_2}^{0,\infty}$. Dividing equation (6.22) by $(1-\delta)$ and equation (6.23) by δ then subtracting the results gives

$$\frac{d}{dt}\left(\frac{\pi_{h_1}^0}{1-\delta} - \frac{\pi_{h_2}^0}{\delta}\right) = -(\mu+\sigma+\eta)\left(\frac{\pi_{h_1}^0}{1-\delta} - \frac{\pi_{h_2}^0}{\delta}\right). \tag{6.70}$$

The general solution to this equation shows that

$$\delta\pi_{h_1}^0 - (1-\delta)\pi_{h_2}^0 \to 0 \text{ as } t \to \infty. \tag{6.71}$$

Hence given $\epsilon > 0$ there exists t_6 such that for $t \geq t_6$, $\delta\pi_{h_1}^0 \leq (1-\delta)\pi_{h_2}^0 + (\epsilon/2)$. In addition, there exists $t_7 \geq t_6$ such that for $t \geq t_7$

$$(1-\delta)\pi_{h_2}^0 \leq (1-\delta)\left(\pi_{h_2}^{0,\infty} + \frac{\epsilon}{2(1-\delta)}\right).$$

Therefore for $t \geq t_7$ we have $\delta\pi_{h_1}^0 \leq (1-\delta)\pi_{h_2}^{0,\infty} + \epsilon$. So

$$\delta\pi_{h_1}^{0,\infty} = \limsup_{t\to\infty} \delta\pi_{h_1}^0 \leq (1-\delta)\pi_{h_2}^{0,\infty} + \epsilon.$$

Since ϵ is arbitrary, we deduce that $\delta\pi_{h_1}^{0,\infty} \leq (1-\delta)\pi_{h_2}^{0,\infty}$. We can use a similar proof to show the reverse inequality and hence the result follows. □

Using this method with equations (6.28) and (6.29) it is straightforward to show that the following result holds:

Lemma 6.14. $(1-\delta)\pi_{h_2}^{1,\infty} = \delta\pi_{h_1}^{1,\infty}$.

Define $\pi_h^0 = \pi_{h_1}^0 + \pi_{h_2}^0$. Using (6.71) it is straightforward to show that $\pi_h^{0,\infty} = \pi_{h_1}^{0,\infty}/(1-\delta) = \pi_{h_2}^{0,\infty}/\delta$. It is similarly straightforward to show that $\pi_h^{1,\infty} = \pi_{h_1}^{1,\infty}/(1-\delta) = \pi_{h_2}^{1,\infty}/\delta$. We can use Lemmas 6.13 and 6.14 to write the inequalities

in Lemmas 6.11 and 6.12 in terms of $\pi_h^{0,\infty}$ and $\pi_h^{1,\infty}$ to obtain:

$$\pi_y^{0,\infty} \leq \frac{\sigma(1-\delta)\pi_h^{0,\infty}}{\mu+\eta}, \tag{6.72}$$

$$\pi_y^{1,\infty} \leq \frac{\sigma(1-\delta)\pi_h^{1,\infty}}{\mu} + \frac{\eta\sigma(1-\delta)\pi_h^{0,\infty}}{\mu(\mu+\eta)}. \tag{6.73}$$

Hence

$$\alpha_h\pi_h^{0,\infty} + \alpha_y\pi_y^{0,\infty} \leq \left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu+\eta}\right)\pi_h^{0,\infty},$$

$$\alpha_h\pi_h^{1,\infty} + \alpha_y\pi_y^{1,\infty} \leq \left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right)\pi_h^{1,\infty} + \frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\pi_h^{0,\infty}.$$

Now we have

$$\begin{aligned}\overline{K}_0 \leq{}& \lambda_0 s_{00}(1-\phi)\psi_0^*\left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu+\eta}\right)\pi_h^{0,\infty} \\ &+ \lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0^*}}{\pi^{1^*}}\left[\left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right)\pi_h^{1,\infty} + \frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\pi_h^{0,\infty}\right],\end{aligned}$$

$$\begin{aligned}\overline{K}_1 \leq{}& \lambda_1 s_{10}(1-\phi)\psi_0^*\frac{\pi^{1^*}}{\pi^{0^*}}\left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu+\eta}\right)\pi_h^{0,\infty} \\ &+ \lambda_1 s_{11}(1-\phi)\psi_1^*\left[\left(\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right)\pi_h^{1,\infty} + \frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\pi_h^{0,\infty}\right].\end{aligned}$$

Substituting in the upper bounds for $\pi_h^{0,\infty}$ and $\pi_h^{1,\infty}$ given by Lemmas 6.9 and 6.10 respectively allows us to write this as a set of simultaneous inequalities satisfied by $\overline{K}_0$ and $\overline{K}_1$. Writing $\overline{\boldsymbol{K}} \leq (\overline{K}_0, \overline{K}_1)$ these inequalities can be written as

$$\overline{\boldsymbol{K}} \leq \mathbf{M}^+(\overline{\boldsymbol{K}})\overline{\boldsymbol{K}},$$

where $\mathbf{M}^+(\overline{\boldsymbol{K}})$ is a strictly positive strictly monotone decreasing function of $\overline{\boldsymbol{K}}$ for $\overline{\boldsymbol{K}} \geq \boldsymbol{0}$ with $M_{ij}^+(\overline{\boldsymbol{K}}) = M_{ij}^+(\overline{K}_0, \overline{K}_1) \geq 0$ and $\mathbf{M}^+(\boldsymbol{0}) = \mathbf{M}(\boldsymbol{0})$, the transpose of the next generation matrix (6.42). Hence, assuming that either $\overline{K}_0 > 0$ or $\overline{K}_1 > 0$ we have

$$\overline{\boldsymbol{K}} < \mathbf{M}^+(\boldsymbol{0})\overline{\boldsymbol{K}}, \tag{6.74}$$

with strict inequality in both components. Since $\boldsymbol{K}$ is a positive vector in (6.74) there exists an $\epsilon > 0$ with

$$\overline{\boldsymbol{K}}(1+\epsilon) < \mathbf{M}(\boldsymbol{0})\overline{\boldsymbol{K}}.$$

Multiplying both sides by $\mathbf{M}(\boldsymbol{0})$ gives

$$\mathbf{M}(\boldsymbol{0})\overline{\boldsymbol{K}}(1+\epsilon) < \mathbf{M}^2(\boldsymbol{0})\overline{\boldsymbol{K}}.$$

This implies that

$$\overline{\boldsymbol{K}}(1+\epsilon)^2 < \mathbf{M}^2(\boldsymbol{0})\overline{\boldsymbol{K}}. \tag{6.75}$$

Iterating gives

$$\overline{\boldsymbol{K}}(1+\epsilon)^n < \mathbf{M}^n(\boldsymbol{0})\overline{\boldsymbol{K}}. \tag{6.76}$$

Taking norms we have

$$|\overline{\boldsymbol{K}}|(1+\epsilon)^n < |\mathbf{M}^n(\boldsymbol{0})\overline{\boldsymbol{K}}| \leq ||\mathbf{M}^n(\boldsymbol{0})||\ |\overline{\boldsymbol{K}}|.$$

This implies that

$$(1+\epsilon)^n < ||\mathbf{M}^n(\boldsymbol{0})||, \quad \text{(since } |\overline{\boldsymbol{K}}| > 0\text{)},$$

Hence

$$(1+\epsilon) < ||\mathbf{M}^n(\boldsymbol{0})||^{\frac{1}{n}}. \tag{6.77}$$

We again use the fact that the spectral radius, ρ, of a matrix $\mathbf{M}$ is given by $\lim_{t\to\infty} ||\mathbf{M}^n||^{\frac{1}{n}}$ (Diekmann and Heesterbeek 2000), we let $n \to \infty$ in (6.77) to obtain

$$\rho(\mathbf{M}(\boldsymbol{0})) \geq 1+\epsilon,$$

where $\rho(\mathbf{M}(\boldsymbol{0}))$ denotes the spectral radius of the matrix $\mathbf{M}(\boldsymbol{0})$. Since the spec-

tral radius of $\mathbf{M}(\boldsymbol{0})$ is equal to the basic reproductive number R_0, the statement above implies that $R_0 \geq 1 + \epsilon$. This is a contradiction and so $\overline{K}_0 = \overline{K}_1 = 0$ allowing us to deduce that $\pi_h^{0,\infty} = 0$ when $R_0 \leq 1$. $\pi_h^{0,\infty} = 0$ implies that $\pi_{h_1}^{0,\infty} = \pi_{h_2}^{0,\infty} = \pi_y^{0,\infty} = \pi_{h_1}^{1,\infty} = \pi_{h_2}^{1,\infty} = \pi_y^{1,\infty} = 0$. It is then straightforward to show that $\pi_{x_1}^0(t), \pi_{h_1}^0(t), \pi_{h_2}^0(t), \pi_y^0(t), \pi_z^0(t), \pi_{x_1}^1(t), \pi_{h_1}^1(t), \pi_{h_2}^1(t), \pi_y^1(t), \pi_z^1(t)$ all approach zero, $\pi_x^0(t)$ approaches $\mu/(\mu + \eta)$ and $\pi_x^1(t)$ approaches $\eta/(\mu + \eta)$ as t becomes large. This completes the proof of the global stability of the DFE when $0 \leq R_0 \leq 1$.

6.7 Conclusion

In order to ensure that prevention measures designed to reduce the burden associated with HCV infection are allocated efficiently, it is important to understand how individuals in the IDU population interact. Studies have suggested that the IDU population can be separated into two risk groups with different risk behaviours (Sutton *et al.* 2006; Roy *et al.* 2007; Mehta *et al.* 2011). Few studies have modelled the spread of HCV among IDUs in this way and demonstrated the potential effectiveness of interventions such as needle exchange and other harm reduction measures (Kretzschmar and Wiessing 2004; Vickerman *et al.* 2007).

In this chapter we have developed a mathematical model that separates our IDU population into two groups by time since onset of injection, building on the models developed by Greenhalgh (1997), Kretzschmar and Wiessing (2004) and Vickerman *et al.* (2009). We have shown analytically that the behaviour of the model is again governed by the basic reproductive number R_0, with $R_0 = 1$ a critical threshold for endemic HCV prevalence. We have shown that if $R_0 \leq 1$ and the disease is initially present in the population, then the system will tend toward the globally stable disease free equilibrium where HCV has been eliminated in all IDUs and needles. If $R_0 > 1$ we have shown that there is a unique endemic equilibrium.

Our analysis of the behaviour of this model is limited because of the complexity of the model. When analysing the simple HCV transmission model in Chapter 3, we were able show that when $R_0 > 1$ the disease would persist in the population and that for a realistic approximation to the basic model the endemic equilibrium was locally stable. In addition, we were able to show that provided

that $R_0 > 1$ and HCV was initially present in the population, the simple model would tend towards the endemic equilibrium, provided that certain conditions were met. While it was not possible to prove similar results for the time since onset of injection model, numerical simulations were used to verify that the time since onset of injection model behaved in a similar way. These simulations form part of our next chapter where we first discuss parameter estimation and then use the numerical simulation package Berkeley Madonna (Macey *et al.* 2000) to examine the spread of HCV amongst Glasgow IDUs.

Chapter 7

A time since onset of injection HCV transmission model: Parameter estimation and numerical simulations

In this chapter we use the simulation package Berkeley Madonna version 8.3.11 (Macey *et al.* 2000) to produce HCV prevalence estimates for the Glasgow IDU population over time given by our model governing equations in Chapter 6. Using Glasgow IDU survey data for the periods 1990-1993 and 2008-2009 supplied by HPS we derive two sets of parameter estimates: one each for IDU behaviour during 1990-1993 and 2008-2009 respectively. We produce HCV prevalence estimates using each parameter set and compare these with the estimated HCV prevalence among IDUs surveyed in Glasgow for each period. We will show that although the model performs well with data from the earlier period, it performs poorly when more recent survey data is used to obtain parameter estimates. Furthermore, since IDUs can have a tendency to under-estimate their needle and syringe sharing behaviour (Greenfield *et al.* 1995) we investigate to what extent this occurs amongst Glasgow IDUs in 2008-2009.

7.1 Parameter estimates

Tables 7.1, 7.2 and 7.3 show the behavioural and biological parameter estimates used in our simulations. We now discuss these estimates used in our simulations with the exception of α, δ, σ and ϕ which remain unchanged from our simple model simulations (see Chapter 4 for discussions on these estimates).

7.1.1 Progression rate between groups (η)

In surveillance reports generated by HPS and colleagues (NESI 2010), when IDUs are separated into two experience groups by time since onset of injection the threshold separating the two groups is either three years or five years. In order to ensure that we have a reasonable number of IDUs in the naive experienced group we decided to define naive IDUs to be those IDUs who have been injecting for five years or less and experienced IDUs to be those IDUs who have been injecting for more than five years. This therefore implies that $1/\eta = 5$ years.

7.1.2 Proportion of IDUs that are naive and experienced injectors (π^0, π^1)

Using survey data from Glasgow IDUs attending needle exchange services during 2008-2009 we estimated the fraction of the population that are naive or experienced injectors. Among the 947 IDUs surveyed in 2008-2009, 704 (74%) IDUs reported injecting drug use in the six month period prior to interview. Of these IDUs, 164 (23%) reported that the time between interview and their first injection was five years or less and 540 (77%) reported that the time between interview and their first injection was more than five years. Of note, young or naive IDUs may be under-represented at needle exchange services. This may be because they lack knowledge of the existence of these services or that they are unwilling to admit that they have injected drugs and therefore are reluctant to attend services. Either way, this could mean that more than 23% of IDUs are naive injectors. Therefore, we estimated that 33.33% of the Glasgow IDU population are naive injectors and 66.67% are experienced injectors for both the 1990-1993 and 2008-2009 periods. In addition, the size of the Glasgow IDU population has been relatively constant over a number of years so we assume that our es-

Parameter	Estimate	Source	Notes
ϕ	0.255	Unpublished data HPS (1990-1993)	Observed data on Glasgow IDUs during 1990-1993
α_y	2.5%	Hutchinson, Bird *et al.* (2006)	Assumption based on observed data on HCV transmission through needle stick injury
α_h	6.75%	Conservative estimate	Estimate is 2.7 $\times\alpha_y$ based on Vickerman *et al.* (2007) model fits
$1/\sigma$	0.5 years	Vickerman *et al.* (2007, 2009)	Observed data from studies on acute HCV
α	0.25	Conservative estimate	Limited data available
δ	0.26	Micallef *et al.* (2006)	Review of longitudinal studies during 1980-2003
$1/\eta$	5 years		Assumption based on surveillance reports of IDUs
$1/\mu$	10.002 years	Calculated estimate	Based on assumed equilibrium proportion of naive IDUs and time since onset of injection
π^0	0.3333†	Unpublished data HPS (2008-2009)	Based on observed data of Glasgow IDUs during 2008-2009
π^1	0.6667†	Unpublished data HPS (2008-2009)	Based on observed data of Glasgow IDUs during 2008-2009

†assumed to be at equilibrium

Table 7.1: Table of baseline parameter estimates for use in the time since onset of injection model.

Parameter	Estimate	Source	Notes
λ_0	45 per IDU per year	Unpublished data HPS (1990-1993)	Observed data on Glasgow IDUs during 1990-1993
λ_1	37 per IDU per year	Unpublished data HPS (1990-1993)	Observed data on Glasgow IDUs during 1990-1993
$365.25/\tau$	15.4 days	Frischer *et al.* (1993); Gruer *et al.* (1993); Taylor *et al.* (2001)	Based on the estimated number of Glasgow IDUs during 1990 and observational data on needle and syringe provision in Glasgow during 1990-1993
s_{00}	0.6667	Conservative estimate	No data
s_{01}	0.3333	Conservative estimate	No data
s_{10}	0.2026	Conservative estimate	No data
s_{11}	0.7974	Conservative estimate	No data

Table 7.2: Table of parameter estimates for the period 1990-1993.

Parameter	Estimate	Source	Notes
λ_0	1.96 per IDU per year	Unpublished data HPS (2008-2009)	Observed data on Glasgow IDUs during 2008-2009
λ_1	2.56 per IDU per year	Unpublished data HPS (2008-2009)	Observed data on Glasgow IDUs during 2008-2009
$365.25/\tau$	3.26 days	Hay *et al.* (2009); ISD Scotland (2010)	Based on the estimated number of Glasgow IDUs during 2008 and observational data on needle and syringe provision in Glasgow during 2008-2009
s_{00}	0.6667	Conservative estimate	No data
s_{01}	0.3333	Conservative estimate	No data
s_{10}	0.1276	Conservative estimate	No data
s_{11}	0.8724	Conservative estimate	No data

Table 7.3: Table of parameter estimates for the period 2008-2009.

timates for π^0 and π^1 are the equilibrium values for these parameters. That is, $\pi^0 = \pi^{0*} = 0.3333$ and $\pi^1 = \pi^{1*} = 0.6667$.

7.1.3 Average length of injecting career $(1/\mu)$

Using equation (6.47) we can estimate the length of injecting career. At equilibrium, the fraction of naive IDUs in the population is given by $\mu/(\mu + \eta)$. Rearranging this for μ and using our estimates for π^{0*} and η we see that $\mu = 0.09998$ IDUs per year. This means that the length of injecting career is approximately ten years. Comparing this estimate with those used in the published literature we see that this estimate has been used by Kaplan and O'Keefe (1993) in their HIV model and Vickerman *et al.* (2007) in their HCV model (see Chapter 4 for detailed discussions). This gives us confidence that our estimate of $\mu = 0.09998$ IDUs per year is reasonable.

7.1.4 Acute and chronic HCV transmission probabilities (α_h, α_y)

When estimating the acute and chronic HCV transmission probabilities for our simple model, we assumed that there was a six to eight week period of high viraemia following HCV infection which was incorporated into a general acute phase. This meant that the effects of the highly infectious period were averaged out over the length of the acute phase and resulted in an acute HCV transmission probability that was greater than that of chronic HCV infection. Moreover, our estimates for these parameters assumed that the transmission probability of acute HCV infection was 2.7 times the transmission probability of chronic HCV infection (see Section 4.3). Our time since onset of injection model maintains these assumptions.

We decided to increase our estimate for the transmission probability of chronic infection from $\alpha_y = 0.016$ to $\alpha_y = 0.025$ to be more in line with the estimates suggested by Crofts *et al.* (1999) (0.013-0.049), Hutchinson, Bird *et al.* (2006) (0.02-0.03) and the Advisory Council on the Misuse of Drugs (2009) (0.015-0.05). Since we are continuing to assume that acute HCV infection is 2.7 times more infectious than chronic infection, our estimate of $\alpha_y = 0.025$ implies that, α_h, the per injection transmission probability of acute HCV infection, is 0.0675.

7.1.5 Average working life of a needle ($365.25/\tau$)

Using a method similar to that used in Chapter 4, we combined data on the size of the injecting population with survey data on the frequency of injecting and needle and syringe distribution for each period to obtain our estimates.

Estimate for 1990-1993

2,038 current IDUs were surveyed in Glasgow in 1990-1993, we estimated that there were a total of 2,299,182 injecting events for this group in 1990-1993, generating an average of 1,128 injections per year per IDU. Frischer *et al.* (1993) estimated that there were approximately 8,500 IDUs in Glasgow during 1990. Assuming that the population size was constant during the survey period and that each of these 8,500 IDUs injected at the rate of 1,128 injections per year, then there were an estimated 9,588,000 injections per year during 1990-1993. From Gruer *et al.* (1993) and Taylor *et al.* (2001) 136,900, 190,000 and 238,500 needles and syringes were distributed in Glasgow during 1990, 1991 and 1992 respectively. Assuming that there were 238,500 needles and syringes distributed during 1993, we calculated that there were an average 200,975 needles and syringes distributed each year during the survey period. Taking the estimated number of injections per year and dividing by the average number of needles distributed each year, we estimated that each needle was used approximately 47.7 times before it was exchanged. Furthermore, if we assume that IDUs inject at a rate of 1,128 injections per year, then IDUs inject on average 3.09 times per day. Therefore, if each needle is used approximately 47.7 times before it is exchanged, with an average injecting frequency of 3.09 times per day then the working life of a single needle is approximately 15.4 days.

Estimate for 2008-2009

From the 704 current IDUs surveyed in Glasgow during June 2008-June 2009 we estimated that there were a total of 325,092 injecting events for this group during June 2008-June 2009, generating an average of 462 injections per year per IDU. Hay *et al.* (2009) estimated that there were approximately 8,862 IDUs in Glasgow in 2006. Assuming that the number of IDUs in Glasgow has remained stable since 2006, and these IDUs have continued to inject at the rate of 462 injections per

year, then there were an estimated 4,094,244 injecting events during the financial year 2008/09. According to provisional estimates from ISD Scotland (2010), 991,875 needles and syringes were distributed in Glasgow during the financial year 2008/09. Hence, we estimated that each needle was used approximately 4.13 times before it was exchanged. Furthermore, if we assume that IDUs inject at a rate of 462 injections per year, then IDUs inject on average 1.26 times per day. Therefore if each needle is used approximately 4.13 times before it is exchanged, with an average injecting frequency of 1.26 times per day then the working life of a single needle is 3.26 days.

7.1.6 Naive and experienced needle and syringe sharing rates (λ_0, λ_1)

Estimate for 1990-1993

Using our definition of naive and experienced IDUs, we found that 649 (32%) of the 2,038 current IDUs surveyed in Glasgow in 1990-1993 were defined as naive injectors with the remaining 1,389 (68%) defined as experienced injectors. We examined the frequency of needle and syringe sharing reported by each group in the six month period prior to interview and estimated that there were 28,884 shared injections per year for the 649 naive IDUs and 51,212 shared injections per year for the 1,389 experienced IDUs. Therefore, the average shared injection rate for naive IDUs (λ_0) is 45 shared injections per IDU per year and the average shared injection rate for experienced IDUs (λ_1) is 37 shared injections per IDU per year for this period.

Estimate for 2008-2009

Using a similar method to that used above, we estimated that there were 318 shared injections per year among the 162 current naive IDUs and 1,370 shared injections per year among the 535 current experienced IDUs surveyed in Glasgow in 2008-2009. Therefore, the average shared injection rate for naive IDUs (λ_0) is 1.96 shared injections per IDU per year and the average shared injection rate for experienced IDUs (λ_1) is 2.56 shared injections per IDU per year for this period.

7.1.7 Fraction of needles that are borrowed within groups (s_{00}, s_{11}) and across groups (s_{01}, s_{10})

As far as we are aware there is no data available to allow us to determine the proportion of sharing that goes on within groups (between two naive or two experienced IDUs) or across groups (between a naive IDU and an experienced IDU). With no information to guide us we assume that IDUs will prefer to borrow equipment from IDUs in the same experience group. However, we have to remember to satisfy the condition on s_{10} and s_{01} given by (A.4). Hence we estimate that for the period 1990-1993 $s_{00} = 0.6667, s_{01} = 0.3333, s_{10} = 0.2026$ and $s_{11} = 0.7974$ and for the period 2008-2009 $s_{00} = 0.6667, s_{01} = 0.3333, s_{10} = 0.1276$ and $s_{11} = 0.8724$.

7.2 Simulation results

Using the baseline set of parameter estimates for each period given in Tables 7.2 and 7.3 along with the parameter estimates in Table 7.1 we simulate the transmission of HCV in our model over a period of 70 years. Initially we assume that 50% of our IDU population are infected with acute HCV (h_1) and no other IDUs are infected. To be more specific, $\pi_x^0(0) = 0.5/3, \pi_{x_1}^0(0) = 0, \pi_{h_1}^0(0) = 0.5/3, \pi_{h_2}^0(0) = 0, \pi_y^0(0) = 0, \pi_z^0(0) = 0, \pi_x^1(0) = 1/3, \pi_{x_1}^1(0) = 0, \pi_{h_1}^1(0) = 1/3, \pi_{h_2}^1(0) = 0, \pi_y^1(0) = 0$ and $\pi_z^1(0) = 0$ where $\pi_x^0(0) = 0$ denotes the fraction of all IDUs that are in the naive experience group and the x-susceptible class at time $t = 0$. Similar definitions exist for the other IDU classes. Note that we are assuming that the proportions of individuals in the naive and experienced groups start at their equilibrium values and condition (A.4) is satisfied. This then implies that the number of needles and syringes in each group remains constant. The prevalence of HCV (which is given by $\pi_{x_1}^0 + \pi_{h_1}^0 + \pi_{h_2}^0 + \pi_y^0 + \pi_z^0 + \pi_{x_1}^1 + \pi_{h_1}^1 + \pi_{h_2}^1 + \pi_y^1 + \pi_z^1$) for each period is shown in Figure 7.1. These initial conditions were chosen since they allow us to see clearly the behaviour of the model under both sets of baseline parameter estimates. From Figure 7.1 we can see that in both cases HCV prevalence eventually reaches a steady state solution. However, it is also clear that our model predicts two entirely different outcomes. When we use the baseline parameter estimates for 1990-1993 (Table 7.2), $R_0 = 3.598 > 1$ and the prevalence of HCV

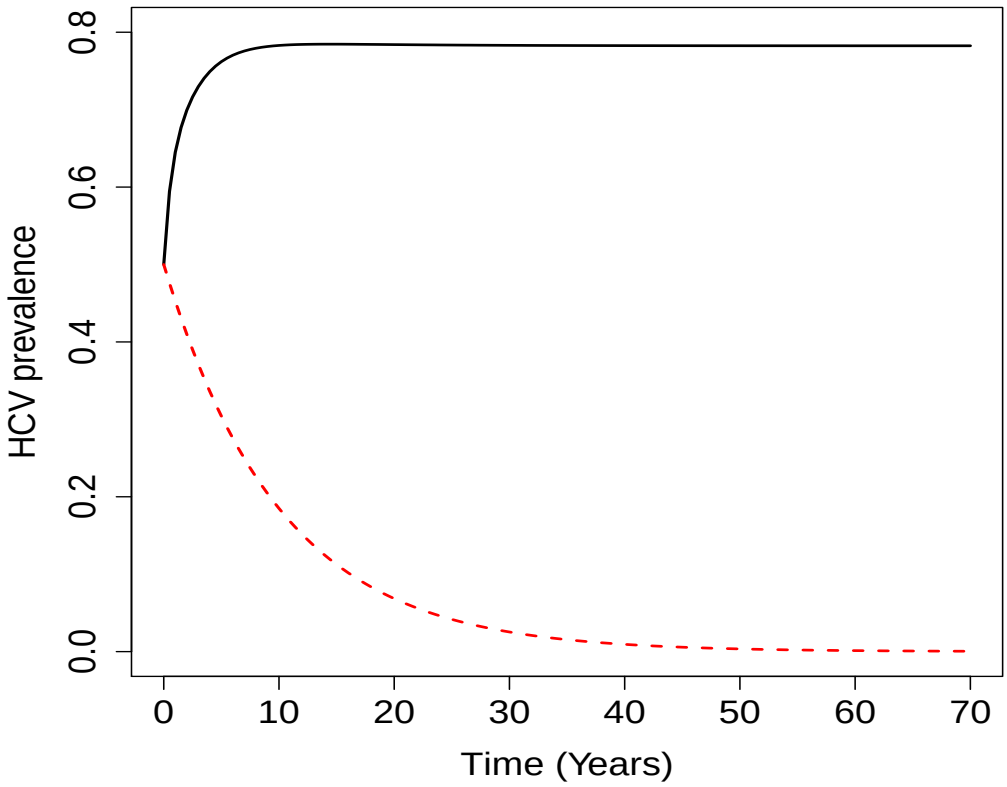

Figure 7.1: HCV prevalence using baseline parameter estimates for 1990-1993 (solid black line) and 2008-2009 (dashed red line).

amongst IDUs in Glasgow reaches an endemic HCV prevalence of approximately 78%. If we run the model using the parameter estimates for 2008-2009 (Table 7.3), $R_0 = 0.009 < 1$ and our predictions suggest that there will be a marked decrease in HCV prevalence amongst Glasgow IDUs which results in eventual HCV elimination.

In order to determine the prevalence of HCV amongst Glasgow IDUs and assess the effectiveness of needle and syringe exchange services, Taylor *et al.* (2000) analysed saliva samples of 1,949 Glasgow IDUs recruited to cross-sectional surveys during 1990-1994 and 1996. To ensure as representative a sample as possible these IDUs were recruited from in-treatment and out-treatment settings. Their analysis showed that 835 (61%) of the 1,363 saliva specimens provided

during 1990-1993 tested positive for HCV antibodies, however, after adjusting for the 85% sensitivity of the saliva test, the overall estimated HCV prevalence amongst Glasgow IDUs during 1990-1993 was 72%. Comparing this estimate for HCV prevalence with the estimate obtained from our model we see that our estimate of 78% is a slight over-estimate for the estimated prevalence at that time. However, given our assumptions we feel that our model performs reasonably well when using the 1990-1993 parameter estimates.

In recent years, IDUs have continually reported low levels of needle and syringe sharing risk behaviour. However, the prevalence of HCV amongst Glasgow IDUs in 2008-2009 was recently estimated as 70% during 2008-2009 (NESI 2010). When using the recent 2008-2009 parameter set we see that our simulations completely contradict the estimated HCV prevalence among Glasgow IDUs and suggest that a marked decrease in HCV prevalence should have been observed in recent years. Since this has clearly not been observed we now examine a possible explanation for the poor fit of our model.

7.3 The level of under-estimation in needle and syringe sharing rates

The idea that IDUs may (either accidentally or deliberately) under-report their needle and syringe risk behaviour is not a new one.

Greenfield *et al.* (1995) examined the validity of self-reported drug use among 281 IDUs by comparing the reported drug use with urine drug test results at four time points during the survey period (at intake and at two, four and six months after intake). The authors reported a significant decrease in the mean number of injections and needle shares over time (Friedman χ^2=80.88, df=8, $p < 0.01$; χ^2=76.58, df=8, $p < 0.01$, respectively) along with an increasing amount of abstinence from injecting drug use. Those IDUs who reported abstinence from injecting drug use had the validity of their self-reported behaviour checked via urinalysis. At intake 160 IDUs provided urine samples. At the six month follow-up interview the number of IDUs reporting abstinence had increased from 58 IDUs at intake to 82 IDUs. However, positive urinalysis indicating drug use did not decline over time and the number of disconfirmed self-reports of abstinence

increased from 3 (5%) at intake to 14 (17%) at month six of follow-up.

This study highlights the possibility that IDUs may under-report their risk behaviour in favour of more socially acceptable responses. The under-reporting of socially sensitive behaviour may be due to the comprehension, concentration and memory of an individual (Copersino *et al.* 2010) or it may be caused by the method of interview.

In a study by des Jarlais *et al.* (1999) 757 IDUs and 724 IDUs were interviewed using face-to-face methods and an audio-computer self interviewing method (audio-CASI) respectively. While the study focused on risk behaviour for HIV, the results showed that significantly more HIV risk behaviour and less protective behaviour was reported when the audio-CASI method was used (odds ratio 1.5 or higher and 0.7 or lower, respectively) ($p < 0.02$), although the authors were unable to validate the reported behaviours in either method. While this study cannot confirm that the audio-CASI method gives a better indication of true risk behaviour, it does highlight the possibility of under-reporting when face-to-face interview techniques are used.

When using the 2008-2009 parameter set our model does not perform as well as it did when the 1990-1993 parameter set was used. One possible reason for this is that IDUs are now more concerned about the perceived social stigma that surrounds certain risk behaviours, thus increasing the level of under-reporting in injecting risk behaviour. We now examine to what extent needle and syringe sharing risk behaviour may be under-estimated among Glasgow IDUs. We modify our governing equations by introducing V_0 and $V_1 = \zeta V_0$ which multiply the estimated needle and syringe sharing rates λ_0 and λ_1 respectively. We aim to find values of V_0 and ζ that result in endemic equilibrium solutions that lie within the 95% confidence interval for HCV prevalence amongst Glasgow IDUs. Initially we assume that $\zeta = 1$ which implies that $V_0 = V_1$ meaning that both naive and experienced IDUs under-estimate their needle and syringe sharing by the same factor. If $\zeta < 1$ then naive IDUs under-estimate their needle and syringe sharing more than experienced IDUs, the opposite is true if $\zeta > 1$. Note that if $\zeta \neq 1$ and we assume that s_{00} and s_{01} are fixed, then we have to alter our baseline estimates for s_{10} and s_{11} in order to satisfy (A.4).

HCV prevalence among Glasgow IDUs is approximately 70% (95% CI 67-73%) (NESI 2010). The factor increase in sharing rates required to achieve an endemic

equilibrium prevalence within this range is shown in Figure 7.2.

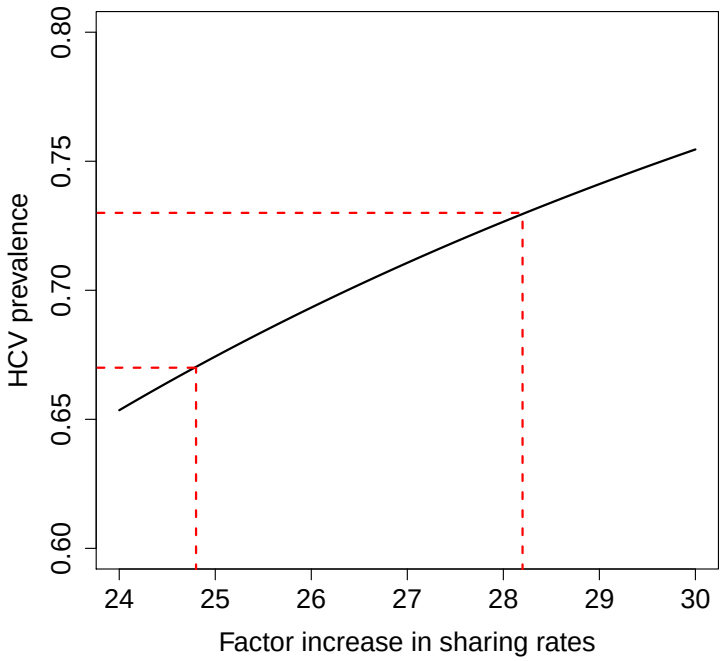

Figure 7.2: Parameter plot showing the factor increase in needle and syringe sharing rates required to achieve HCV prevalence of 67-73%.

From Figure 7.2 we can clearly see that a factor increase in needle and syringe sharing rates of approximately 24.8-28.2 results in an HCV prevalence between 67-73%. This allows us to deduce that if naive and experienced IDUs under-estimate by the same factor then the true needle and syringe sharing rates are somewhere between 24.8 and 28.2 times higher than are being reported. These figures imply that the needle and syringe sharing rate for naive IDUs must increase from 1.96 sharing events per IDU per year to somewhere between 48.6 and 55.3 sharing events per IDU per year. Similarly, the needle and syringe sharing rate for experienced IDUs must increase from 2.56 sharing events per IDU per year to somewhere between 63.5 and 72.2 sharing events per IDU per year. In addition, these figures imply that R_0, the basic reproductive number for HCV amongst Glasgow IDUs, is somewhere between 2.60 and 3.22.

We now check the assumption that both naive and experienced injectors under-estimate by the same factor which lies between 24.8 and 28.2 (Figure 7.3).

Using these values in the model we simulate the behaviour of the model over a period of 70 years. Initially we assume that 1% of our IDU population is in the acute (h_1) infection stage and that one third of those infected IDUs are naive injectors with the remaining two thirds comprised of experienced injectors. To be more specific, $\pi_x^0(0) = 0.33, \pi_{x_1}^0(0) = 0, \pi_{h_1}^0(0) = 0.0033, \pi_{h_2}^0(0) = 0, \pi_y^0(0) = 0, \pi_z^0(0) = 0, \pi_x^1(0) = 0.66, \pi_{x_1}^1(0) = 0, \pi_{h_1}^1(0) = 0.0067, \pi_{h_2}^1(0) = 0, \pi_y^1(0) = 0$ and $\pi_z^1(0) = 0$.

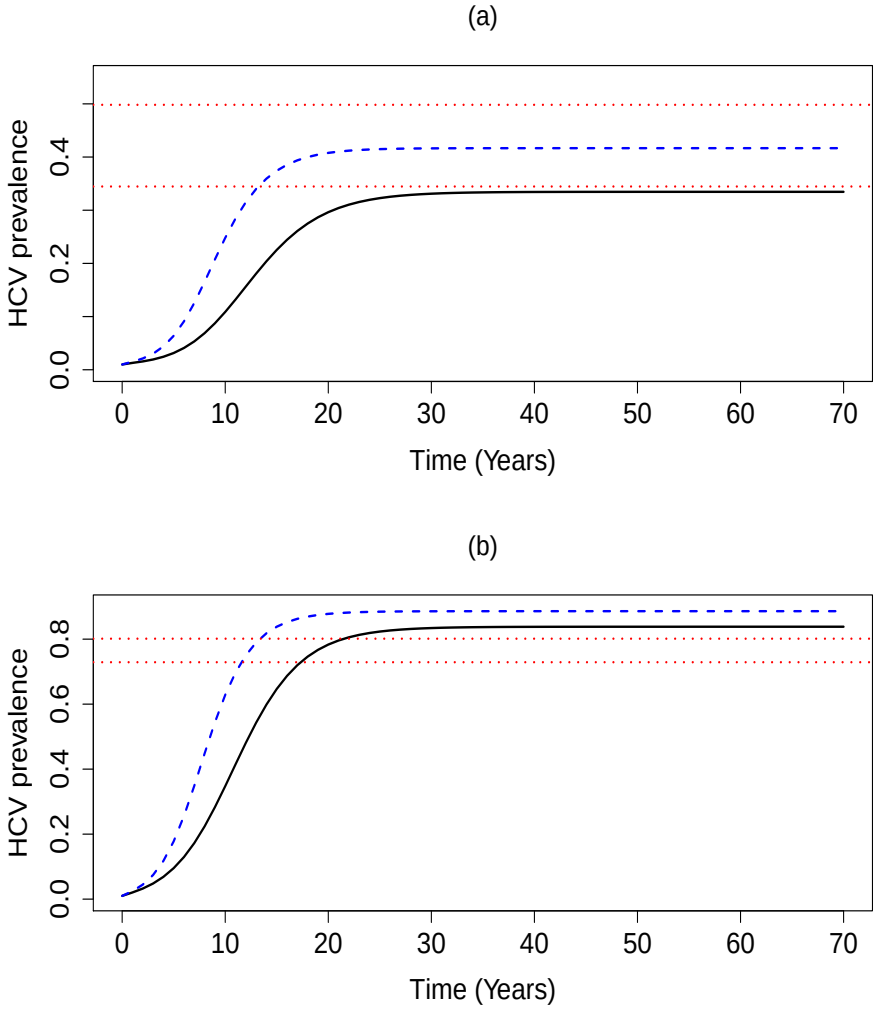

Figure 7.3: HCV prevalence for (a) naive IDUs and (b) experienced IDUs when sharing is increased by a factor of 24.8 (solid black lines) and 28.2 (dashed blue lines). The 95% CIs for the observed HCV prevalence from a survey of naive IDUs (34.5-49.9%) and experienced IDUs (72.9-80.1%) are shown in red.

From Figure 7.3(a) we find that a factor increase in sharing rates of between 24.8 and 28.2 implies that the prevalence of HCV amongst naive IDUs lies between 33.4% to 41.2%. This straddles the 95% CI for the observed prevalence of HCV from a survey of naive IDUs in Glasgow (34.5-49.9%). A factor increase in sharing rates of between 24.8 and 28.2 implies that the prevalence of HCV amongst experienced IDUs lies between 83.8% to 88.6% (Figure 7.3(b)); these estimates are greater than the 95% CI for the observed prevalence estimate for this group (72.9-80.1%). There may be multiple reasons for this over-estimation. But if experienced IDUs are more likely to report risk behaviours than naive IDUs then we may have over-estimated the factor by which experienced IDUs under-report needle and syringe sharing rates. This in turn would result in an over-estimation of HCV prevalence among experienced IDUs.

We are now going to investigate how the level of under-estimation differs between naive and experienced IDUs. To do this we will use the curve fit tool in Berkeley Madonna (which uses the method of least squares to find parameter estimates) to alter both V_0 and ζ simultaneously and fit the endemic HCV prevalence of our model, which occurs when $t > 60$ years, to the HCV prevalence observed in surveys of naive and experienced IDUs. Hence we will fit our model to a naive HCV prevalence of 42.2% and an experienced HCV prevalence of 76.5%. In doing so we modify our baseline parameter estimates for s_{10} and s_{11} to ensure that condition (A.4) is satisfied.

Figure 7.4 shows our simulated prevalence of HCV amongst all IDUs in Glasgow after we have performed our curve fit and Table 7.4 summarises the results. From the figure we can see that fitting our model to observed naive and experienced HCV prevalence estimates results in a HCV prevalence amongst all IDUs of approximately 65%. Therefore, our model under-estimates the lower 95% CI estimate for the observed HCV prevalence amongst Glasgow IDUs by approximately 2%.

From Table 7.4 we can see that there is a substantial under-reporting in needle and syringe sharing rates, factors of approximately 34 for naive IDUs and approximately 17 for experienced IDUs. These results suggest that naive IDUs are more likely to under-report their true needle and syringe sharing risk behaviour. However, it is clear that experienced IDUs may also reduce their levels of risk behaviour when interviewed in order to present themselves as more socially

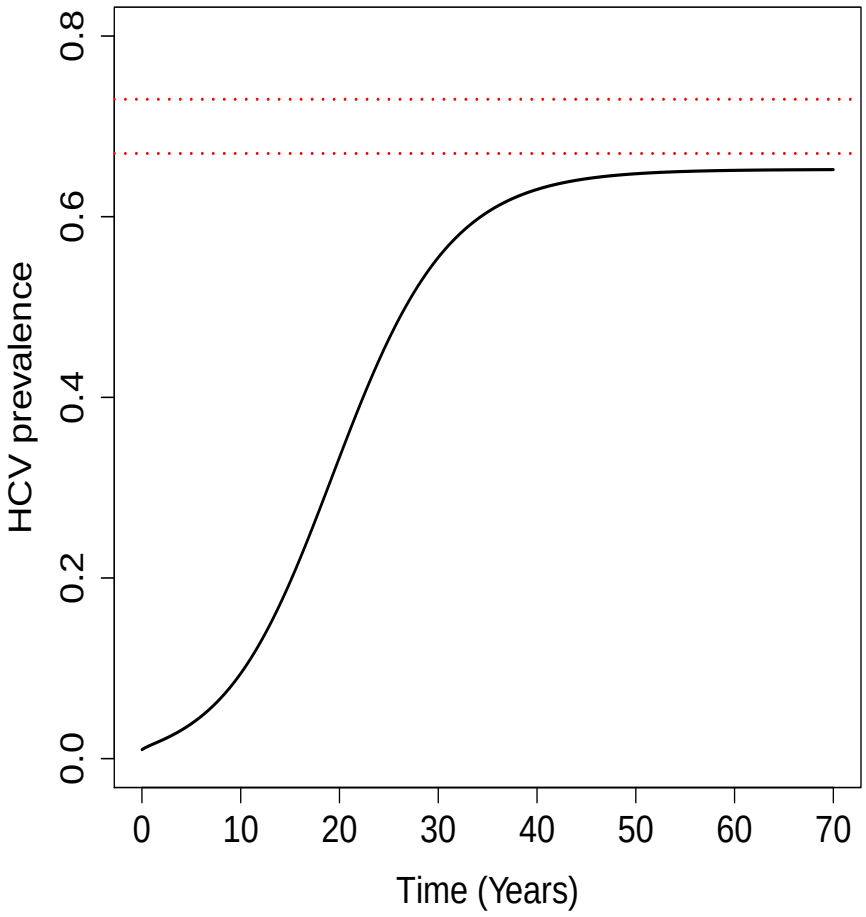

Figure 7.4: HCV prevalence amongst Glasgow IDUs when the model is fitted to the observed HCV prevalence estimates for both naive and experienced IDUs. Here, $\lambda_0 = 66.79$ per IDU per year, $\lambda_1 = 42.32$ per IDU per year, $s_{10} = 0.263$, $s_{11} = 0.737$. The 95% CIs for the observed prevalence of HCV amongst Glasgow IDUs (67-73%) are shown in red.

acceptable. Furthermore, our results suggest that the basic reproductive number of HCV in Glasgow is approximately 2.165.

	Curve fit
Observed prevalences for fit (naive,experienced)	(42.2%, 76.5%)
V_0	34.075
V_1	16.531
λ_0* ($1.96V_0$)	66.79
λ_1* ($2.56V_1$)	42.32
s_{10}	0.263
s_{11}	0.737
Modelled prevalence in Glasgow (%)	65.2
R_0	2.165

*rates are per IDU per year.

Table 7.4: Summary of results obtained with model curve fit.

7.4 Conclusions

In this chapter we analysed the behaviour of our model over time using the numerical simulation package Berkeley Madonna version 8.3.11 (Macey *et al.* 2000). We initially used two parameter sets: one from 1990-1993 and one from 2008-2009. We showed that while our model performed reasonably well when the 1990-1993 parameter set was used, performance was poor when the 2008-2009 parameter set was used. We speculated that an under-estimation in the self-reported needle and syringe sharing rates, which were used to obtain our parameter estimates, could explain the poor performance of our model.

We then examined to what extent that naive and experienced IDUs under-report their needle and syringe sharing risk behaviour. Our simulations suggested that naive and experienced IDUs under-report their sharing risk behaviour by different amounts, with naive IDUs under-reporting more than experienced IDUs. In fact, the results suggest that naive IDUs could be under-reporting their needle and syringe sharing by a factor of 34. This means that there are approximately 66.79 needle and syringe sharing events per year per naive IDU on average. This is a substantial increase on the reported 1.96 sharing events per IDU per year in 2008-2009. Similarly, there are at least 42.32 sharing events per experienced IDU per year which is again more than the reported sharing levels of 2.56 per experienced IDU per year. Since self-reported risk behaviour is one way of evaluating the effectiveness of intervention measures, these figures highlight how researchers

and policy makers need to be aware of the potential bias in this method of evaluation.

High levels of risk behaviour are often associated with naive injectors (Cassin *et al.* 1998; Hahn *et al.* 2002; Mathei *et al.* 2008). Hence, one would expect naive injectors to have higher levels of needle and syringe sharing. Examining the baseline parameter set for 1990-1993 we see that this is indeed the case. However, the 2008-2009 parameter set suggests that naive IDUs share needles and syringes less than experienced IDUs. When we applied our curve fitting techniques we found that naive IDUs would have sharing rates that are greater than the sharing rates for experienced IDUs, which is more in line with our expectations.

There is some uncertainty as to whether the under-reporting of needle and syringe sharing is the explanation for the poor model fit to the 2008-2009 data set. In the next chapter we explore another possible source of HCV transmission namely the sharing of HCV contaminated filters.

Chapter 8

Investigation into the risks associated with the sharing of paraphernalia

In resource-rich countries, the sharing of contaminated needles and syringes is considered to have the greatest contribution to HCV transmission. However, there is evidence to show that IDUs also share other injecting paraphernalia (such as cookers, spoons, filters and water) in the process of preparing drugs for injection (Koester 1996; Speed 1998; Gaskin *et al.* 2000; NESI 2010). While the sharing of paraphernalia has not received the attention that the sharing of needles and syringes has, there is now some evidence to suggest that the collective use of drug preparation equipment risks the contamination of the syringe of each injector and thus may be another source of HCV transmission.

Crofts *et al.* (2000) studied used injecting equipment (needles and syringes and other paraphernalia) from ten injecting settings for the presence of HCV RNA. Using laboratory testing the authors found that it was possible to detect HCV RNA on items other than needles and syringes. The results showed that 40% (2/5) of filters, 67% (6/9) of swabs, 25% (1/4) of spoons and 33% (1/3) of water samples had detectable levels of HCV RNA, highlighting the possible risk of HCV transmission through the sharing of these items.

The Risk Activity Variables, Epidemiology and Network Study (RAVEN Study) was a cohort study which assessed whether HBV and HCV incidence

was associated with a Seattle syringe exchange program. From a cohort of 507 HCV Ab-negative IDUs enrolled in the RAVEN study between June 1994 and May 1997, Hagan *et al.* (2001) completed a follow-up of 317 (62.5%) IDUs. Of the 123 IDUs who did not report sharing needles and syringes during the follow-up period (one year from intake) 11 (8.9%) IDUs became HCV Ab-positive. Furthermore, the authors report that the risk ratio for cooker (spoon) and cotton (filter) sharing (defined as the proportion of cooker and cotton sharing IDUs who seroconvert divided by the proportion of non cooker and cotton sharing IDUs who seroconvert) among non needle and syringe sharing IDUs was 3.8 (95% CI 1.1-13.8), which they suggest shows a substantial risk of HCV associated with the sharing of cookers and cotton.

Mathei *et al.* (2006) analysed HCV seroprevalence data on 421 IDUs recruited in 1995 and 1999-2000. A total of 325 IDUs (77.2%) were found to be HCV Ab-positive. The authors found that there was a significant association between HCV infection status and the sharing of paraphernalia ($\chi^2 = 11.54$, $p = 0.007$) and estimated an odds ratio of 2.44 (95% CI 1.44-4.12) between HCV infection status and the sharing of paraphernalia. The authors suggest that these results highlight that the sharing of injecting paraphernalia can contribute substantially to the spread of HCV amongst IDUs.

De *et al.* (2008) also suggested that there could be a risk of infection associated with injecting paraphernalia. In their systematic review the authors identified ten studies that examined HCV incidence and its association with injecting paraphernalia. These papers, primarily looking at North American IDUs, involved IDU cohorts containing between 106 to 543 subjects, the majority of whom were under 30 years of age. The results of this review suggest that the relative risk between infection status and paraphernalia is between 2.0 and 5.9; however, the large confidence intervals surrounding the risk estimates (95% CI range 0.10-31.67) make it difficult to accurately determine the risk.

While relatively few (93 IDUs, 13%) of the 704 IDUs interviewed in 2008-2009 in Glasgow reported sharing of needles and syringes in the six month period prior to interview, a higher proportion reported sharing of other paraphernalia in the six month period prior to interview (334 IDUs, 48%) (NESI 2010). This may be because the sharing of paraphernalia is seen more as a social norm or part of the injecting process rather than a risk behaviour. That said, the role that the

sharing of drug preparation equipment plays in disease transmission is not fully understood.

In the previous chapter we assumed that an under-reporting of needle and syringe sharing rates caused our time since onset of injection model to underestimate HCV prevalence rates observed through surveys of IDUs. In this chapter we are going to extend the model in Chapter 6 to allow for HCV transmission through the sharing of paraphernalia. We first derive the governing equations for this extended version of the model. Then, using Berkeley Madonna version 8.3.11 (Macey *et al.* 2000) we aim to estimate the probability of (acute and chronic) HCV transmission through (i) filter sharing, (ii) filter and cooker or spoon sharing and (iii) filter, cooker or spoon and water sharing. In all cases we assume that IDUs do not under-report their needle and syringe sharing and hence the sharing of filters (or filters and cookers or spoons) is the only possible extra source of transmission.

8.1 Model description

We extend the model described in Chapter 6 to allow HCV transmission to occur through the sharing of both needles and syringes and filters.

8.1.1 IDU equations

We first extend the IDU equations given by equations (6.20)-(6.31) to allow for HCV transmission through the sharing of HCV contaminated filters. Let $\chi^i_{h_1}, \chi^i_{h_2}$ and χ^i_y denote the fraction of filters that were last used by a naive ($i = 0$) or experienced ($i = 1$) user, which are respectively in the acute h_1, acute h_2 and chronic y infectious stages at time t. In addition, let λ_{0F}, λ_{1F} denote the average filter sharing rate for naive and experienced IDUs respectively, $\overline{s}_{jk}$ denote the fraction of filters that IDUs in group j borrow from IDUs in group k and α_{hF}, α_{yF} denote the transmission probability of acute and chronic HCV through the sharing of filters respectively. Using a similar method to that already used in Chapters 3, 5 and 6 we find that

$$\begin{aligned}\frac{d\pi_x^0}{dt} &= \mu - (\mu+\eta)\pi_x^0 - f_0\pi_x^0 - \lambda_{0F}\overline{s}_{00}\pi_x^0\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)+\alpha_{yF}\chi_y^0\big)\\ &\quad - \lambda_{0F}\overline{s}_{01}\pi_x^0\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big),\end{aligned} \tag{8.1}$$

$$\begin{aligned}\frac{d\pi_{x_1}^0}{dt} &= \sigma(1-\alpha)\pi_{h_2}^0 - f_0\pi_{x_1}^0 - \lambda_{0F}\overline{s}_{00}\pi_{x_1}^0\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)+\alpha_{yF}\chi_y^0\big)\\ &\quad - \lambda_{0F}\overline{s}_{01}\pi_{x_1}^0\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big) - (\mu+\eta)\pi_{x_1}^0,\end{aligned} \tag{8.2}$$

$$\begin{aligned}\frac{d\pi_{h_1}^0}{dt} &= f_0(1-\delta)(\pi^0-\pi_{h_1}^0-\pi_{h_2}^0-\pi_y^0-\pi_z^0)\\ &\quad + (1-\delta)(\pi^0-\pi_{h_1}^0-\pi_{h_2}^0-\pi_y^0-\pi_z^0)\big[\lambda_{0F}\overline{s}_{00}\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)\\ &\quad + \alpha_{yF}\chi_y^0\big)+\lambda_{0F}\overline{s}_{01}\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big)\big] - (\mu+\sigma+\eta)\pi_{h_1}^0,\end{aligned} \tag{8.3}$$

$$\begin{aligned}\frac{d\pi_{h_2}^0}{dt} &= f_0\delta(\pi^0-\pi_{h_1}^0-\pi_{h_2}^0-\pi_y^0-\pi_z^0)\\ &\quad + \delta(\pi^0-\pi_{h_1}^0-\pi_{h_2}^0-\pi_y^0-\pi_z^0)\big[\lambda_{0F}\overline{s}_{00}\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)+\alpha_{yF}\chi_y^0\big)\\ &\quad + \lambda_{0F}\overline{s}_{01}\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big)\big] - (\mu+\sigma+\eta)\pi_{h_2}^0,\end{aligned} \tag{8.4}$$

$$\frac{d\pi_y^0}{dt} = \sigma\pi_{h_1}^0 - (\mu+\eta)\pi_y^0, \tag{8.5}$$

$$\frac{d\pi_z^0}{dt} = \sigma\alpha\pi_{h_2}^0 - (\mu+\eta)\pi_z^0, \tag{8.6}$$

$$\begin{aligned}\frac{d\pi_x^1}{dt} &= \eta\pi_x^0 - \mu\pi_x^1 - f_1\pi_x^1 - \lambda_{1F}\overline{s}_{10}\pi_x^1\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)+\alpha_{yF}\chi_y^0\big)\\ &\quad - \lambda_{1F}\overline{s}_{11}\pi_x^1\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big),\end{aligned} \tag{8.7}$$

$$\begin{aligned}\frac{d\pi_{x_1}^1}{dt} &= \eta\pi_{x_1}^0 + \sigma(1-\alpha)\pi_{h_2}^1 - f_1\pi_{x_1}^1 - \lambda_{1F}\overline{s}_{10}\pi_{x_1}^1\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)+\alpha_{yF}\chi_y^0\big)\\ &\quad - \lambda_{1F}\overline{s}_{11}\pi_{x_1}^1\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big) - \mu\pi_{x_1}^1,\end{aligned} \tag{8.8}$$

$$\begin{aligned}\frac{d\pi_{h_1}^1}{dt} &= \eta\pi_{h_1}^0 + f_1(1-\delta)(\pi^1-\pi_{h_1}^1-\pi_{h_2}^1-\pi_y^1-\pi_z^1)\\ &\quad + (1-\delta)(\pi^1-\pi_{h_1}^1-\pi_{h_2}^1-\pi_y^1-\pi_z^1)\big[\lambda_{1F}\overline{s}_{10}\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)\\ &\quad + \alpha_{yF}\chi_y^0\big)+\lambda_{1F}\overline{s}_{11}\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big)\big] - (\mu+\sigma)\pi_{h_1}^1,\end{aligned} \tag{8.9}$$

$$\begin{aligned}\frac{d\pi_{h_2}^1}{dt} &= \eta\pi_{h_2}^0 + f_1\delta(\pi^1-\pi_{h_1}^1-\pi_{h_2}^1-\pi_y^1-\pi_z^1)\\ &\quad + \delta(\pi^1-\pi_{h_1}^1-\pi_{h_2}^1-\pi_y^1-\pi_z^1)\big[\lambda_{1F}\overline{s}_{10}\big(\alpha_{hF}(\chi_{h_1}^0+\chi_{h_2}^0)+\alpha_{yF}\chi_y^0\big)\\ &\quad + \lambda_{1F}\overline{s}_{11}\big(\alpha_{hF}(\chi_{h_1}^1+\chi_{h_2}^1)+\alpha_{yF}\chi_y^1\big)\big] - (\mu+\sigma)\pi_{h_2}^1,\end{aligned} \tag{8.10}$$

$$\frac{d\pi_y^1}{dt} = \eta\pi_y^0 + \sigma\pi_{h_1}^1 - \mu\pi_y^1, \tag{8.11}$$

$$\frac{d\pi_z^1}{dt} = \eta\pi_z^0 + \sigma\alpha\pi_{h_2}^1 - \mu\pi_z^1, \tag{8.12}$$

where $\pi_j^i \geq 0$, $\sum_j \pi_j^0 + \sum_j \pi_j^1 = 1$ $(j = x, x_1, h_1, h_2, y, z)$ and f_0, f_1 are given by $f_i = \lambda_i(1-\phi)s_{i0}\frac{\psi_0}{\pi^0}\big(\alpha_h(\pi_{h_1}^0 + \pi_{h_2}^0) + \alpha_y\pi_y^0\big) + \lambda_i(1-\phi)s_{i1}\frac{\psi_1}{\pi^1}\big(\alpha_h(\pi_{h_1}^1 + \pi_{h_2}^1) + \alpha_y\pi_y^1\big)$.

8.1.2 Derivation of filter equations

We now derive equations that describe the behaviour of filters over time. This process is similar to the one used when deriving the needle equations for the IDU and needle version of the model (see Subsection 6.2.1).

Let F_0 be the number of naive filters in circulation. By naive filters we mean filters which were either last used by a naive IDU or are the last in a sequence of unused exchanged filters, the first of which was exchanged for a filter last used by a naive IDU. If for simplicity of exposition we assume that all IDUs borrow filters immediately before they use them then the group of naive filters is exactly those filters in circulation in the current possession of a naive IDU. Let F_1 denote the corresponding quantity for experienced filters. At time t, the total rate at which needles and syringes in the naive group are used is given by

$$(\overline{\Lambda}_{00} + \overline{\Lambda}_{10})F_0 = \lambda_{0F}\overline{s}_{00}n_0 + \lambda_{1F}\overline{s}_{10}n_1,$$

where n_0 and n_1 are respectively the number of naive and experienced IDUs and $\overline{\Lambda}_{jk} = \frac{\lambda_{jF}\overline{s}_{jk}n_j}{F_k}$, $j, k = 0, 1$, denotes the rate at which an IDU in group j picks up a filter that was last used by a group k IDU. Also the total rate at which filters in the F_0 group are used or exchanged is given by

$$(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)F_0,$$

where τ_f denotes the average rate at which filters are changed for new ones. Hence the probability of choosing an unexchanged filter from the filters currently in the

possession of a naive IDU is given by

$$\overline{\psi}_0 = \frac{\overline{\Lambda}_{00} + \overline{\Lambda}_{10}}{(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)}.$$

Similarly, the probability of choosing an unexchanged filter from the filters currently in the possession of an experienced IDU is given by

$$\overline{\psi}_1 = \frac{\overline{\Lambda}_{11} + \overline{\Lambda}_{01}}{(\overline{\Lambda}_{11} + \overline{\Lambda}_{01} + \tau_f)}.$$

$F_0\chi^0_{h_1}(t + \Delta t)$, the number of naive acute h_1 infected filters at time $t + \Delta t$

$=$ the number of acute h_1 infected filters at time t
$+$ (the number of naive non acute h_1 infected filters at time t) $\times$
(the fraction used by naive acute h_1 IDUs in $[t,\ t{+}\Delta t)$)
$-$ (the number of naive acute h_1 infected filters at time t) $\times$
(the fraction used by naive non acute h_1 IDUs in $[t,\ t{+}\Delta t)$)
$+$ the number of experienced filters at time t last used by a naive acute h_1 infected IDU in $[t,\ t{+}\Delta t)$
$-$ the number of naive acute h_1 filters at time t used by experienced IDUs in $[t,\ t{+}\Delta t)$
$-$ the number of naive acute h_1 filters exchanged in $[t,\ t{+}\Delta t)$.

Thus we have

$$F_0\chi^0_{h_1}(t + \Delta t) = F_0\chi^0_{h_1}(t) + \overline{\Lambda}_{00}\left(\frac{\pi^0_{h_1}}{\pi^0}F_0\big(1 - \chi^0_{h_1}\big) - \frac{\pi^0 - \pi^0_{h_1}}{\pi^0}F_0\chi^0_{h_1}\right)\Delta t$$
$$+ \overline{\Lambda}_{01}\frac{\pi^0_{h_1}}{\pi^0}F_1\Delta t - \overline{\Lambda}_{10}F_0\chi^0_{h_1}\Delta t - F_0\chi^0_{h_1}\tau_f\Delta t + o(\Delta t).$$

Subtracting $F_0\chi^0_{h_1}(t)$ from both sides, dividing by Δt then letting $\Delta t \to 0$ gives

$$F_0\frac{d\chi^0_{h_1}}{dt} = \big(F_0\overline{\Lambda}_{00} + F_1\overline{\Lambda}_{01}\big)\frac{\pi^0_{h_1}}{\pi^0} - F_0(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)\chi^0_{h_1}. \tag{8.13}$$

Similarly, for the other infectious filter groups we have

$$F_0\frac{d\chi^0_{h_2}}{dt} = \big(F_0\overline{\Lambda}_{00} + F_1\overline{\Lambda}_{01}\big)\frac{\pi^0_{h_2}}{\pi^0} - F_0(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)\chi^0_{h_2}, \tag{8.14}$$

$$F_0\frac{d\chi^0_{y}}{dt} = \big(F_0\overline{\Lambda}_{00} + F_1\overline{\Lambda}_{01}\big)\frac{\pi^0_{y}}{\pi^0} - F_0(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)\chi^0_{y}, \tag{8.15}$$

$$F_1\frac{d\chi^1_{h_1}}{dt} = \big(F_1\overline{\Lambda}_{11} + F_0\overline{\Lambda}_{10}\big)\frac{\pi^1_{h_1}}{\pi^1} - F_1(\overline{\Lambda}_{11} + \overline{\Lambda}_{01} + \tau_f)\chi^1_{h_1}, \tag{8.16}$$

$$F_1\frac{d\chi^1_{h_2}}{dt} = \big(F_1\overline{\Lambda}_{11} + F_0\overline{\Lambda}_{10}\big)\frac{\pi^1_{h_2}}{\pi^1} - F_1(\overline{\Lambda}_{11} + \overline{\Lambda}_{01} + \tau_f)\chi^1_{h_2}, \tag{8.17}$$

$$F_1\frac{d\chi^1_{y}}{dt} = \big(F_1\overline{\Lambda}_{11} + F_0\overline{\Lambda}_{10}\big)\frac{\pi^1_{y}}{\pi^1} - F_1(\overline{\Lambda}_{11} + \overline{\Lambda}_{01} + \tau_f)\chi^1_{y}, \tag{8.18}$$

The approximation argument that was used in the local stability analysis of the endemic equilibrium of the simple model (Theorem 3.5) and the development of our time since onset of injection model (Chapter 6) shows that it is possible to have an approximately valid IDU only model which has the same basic reproductive number and equilibrium values as the full model. Using a similar argument, we approximate the dynamic relationship between the IDU and filter classes by observing that an IDU injects on a timescale that is in the order of days where the epidemiological and demographic changes are much slower and measured in years. Examining equation (8.13) we can see that if the prevalence of HCV is constant among each group of the IDU population, and the size of the naive IDU group and the two filter population group sizes are constant then HCV prevalence in the $\chi^0_{h_1}$ group of needles will tend to

$$\frac{F_0\overline{\Lambda}_{00} + F_1\overline{\Lambda}_{01}}{F_0(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)}\frac{\pi^0_{h_1}}{\pi^0} = \frac{\overline{\Lambda}_{00} + \overline{\Lambda}_{10}}{(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)}\frac{\pi^0_{h_1}}{\pi^0}, \tag{8.19}$$

and we can approximate $\chi^0_{h_1}$ by this limiting value. Using equations (8.14)-(8.18) we can obtain similar expressions for the other filter classes:

$$\chi^0_{h_2} \approx \frac{\overline{\Lambda}_{00} + \overline{\Lambda}_{10}}{(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)}\frac{\pi^0_{h_2}}{\pi^0}, \tag{8.20}$$

$$\chi^0_{y} \approx \frac{\overline{\Lambda}_{00} + \overline{\Lambda}_{10}}{(\overline{\Lambda}_{00} + \overline{\Lambda}_{10} + \tau_f)}\frac{\pi^0_{y}}{\pi^0}, \tag{8.21}$$

$$\chi^1_{h_1} \approx \frac{\overline{\Lambda}_{11} + \overline{\Lambda}_{01}}{(\overline{\Lambda}_{11} + \overline{\Lambda}_{01} + \tau_f)} \frac{\pi^1_{h_1}}{\pi^1}, \tag{8.22}$$

$$\chi^1_{h_2} \approx \frac{\overline{\Lambda}_{11} + \overline{\Lambda}_{01}}{(\overline{\Lambda}_{11} + \overline{\Lambda}_{01} + \tau_f)} \frac{\pi^1_{h_2}}{\pi^1}, \tag{8.23}$$

$$\chi^1_{y} \approx \frac{\overline{\Lambda}_{11} + \overline{\Lambda}_{01}}{(\overline{\Lambda}_{11} + \overline{\Lambda}_{01} + \tau_f)} \frac{\pi^1_{y}}{\pi^1}. \tag{8.24}$$

Substituting (8.19)-(8.24) into equations (8.1)-(8.12) allows us to maintain the IDU only framework of our model. Note that we can use a similar method to that used in Appendix (A.1) to show that in order to prevent one of the filter groups from eventually becoming negative we must satisfy the following condition:

$$\lambda_{0F}\overline{s}_{01}\mu = \lambda_{1F}\overline{s}_{10}\eta. \tag{8.25}$$

8.2 Governing equations

The governing equations for our extended time since onset of injection model are given by

$$\frac{d\pi^0_x}{dt} = \mu - (\mu + \eta)\pi^0_x - f_0\pi^0_x - \underline{f}_0\pi^0_x, \tag{8.26}$$

$$\frac{d\pi^0_{x_1}}{dt} = \sigma(1-\alpha)\pi^0_{h_2} - (\mu + \eta)\pi^0_{x_1} - f_0\pi^0_{x_1} - \underline{f}_0\pi^0_{x_1}, \tag{8.27}$$

$$\begin{aligned}\frac{d\pi^0_{h_1}}{dt} &= f_0(1-\delta)(\pi^0 - \pi^0_{h_1} - \pi^0_{h_2} - \pi^0_y - \pi^0_z) \\ &+ \underline{f}_0(1-\delta)(\pi^0 - \pi^0_{h_1} - \pi^0_{h_2} - \pi^0_y - \pi^0_z) - (\mu + \sigma + \eta)\pi^0_{h_1},\end{aligned} \tag{8.28}$$

$$\begin{aligned}\frac{d\pi^0_{h_2}}{dt} &= \delta f_0(\pi^0 - \pi^0_{h_1} - \pi^0_{h_2} - \pi^0_y - \pi^0_z) + \underline{f}_0\delta(\pi^0 - \pi^0_{h_1} - \pi^0_{h_2} - \pi^0_y - \pi^0_z) \\ &- (\mu + \sigma + \eta)\pi^0_{h_2},\end{aligned} \tag{8.29}$$

$$\frac{d\pi^0_y}{dt} = \sigma\pi^0_{h_1} - (\mu + \eta)\pi^0_y, \tag{8.30}$$

$$\frac{d\pi^0_z}{dt} = \sigma\alpha\pi^0_{h_2} - (\mu + \eta)\pi^0_z, \tag{8.31}$$

$$\frac{d\pi^1_x}{dt} = \eta\pi^0_x - \mu\pi^1_x - f_1\pi^1_x - \underline{f}_1\pi^1_x, \tag{8.32}$$

$$\frac{d\pi^1_{x_1}}{dt} = \eta\pi^0_{x_1} + \sigma(1-\alpha)\pi^1_{h_2} - \mu\pi^1_{x_1} - f_1\pi^1_{x_1} - \underline{f}_1\pi^1_{x_1}, \tag{8.33}$$

$$\frac{d\pi^1_{h_1}}{dt} = \eta\pi^0_{h_1} + f_1(1-\delta)(\pi^1 - \pi^1_{h_1} - \pi^1_{h_2} - \pi^1_y - \pi^1_z) + \underline{f}_1(1-\delta)(\pi^1 - \pi^1_{h_1} - \pi^1_{h_2} - \pi^1_y - \pi^1_z) - (\mu+\sigma)\pi^1_{h_1}, \tag{8.34}$$

$$\frac{d\pi^1_{h_2}}{dt} = \eta\pi^0_{h_2} + \delta f_1(\pi^1 - \pi^1_{h_1} - \pi^1_{h_2} - \pi^1_y - \pi^1_z) + \underline{f}_1(1-\delta)(\pi^1 - \pi^1_{h_1} - \pi^1_{h_2} - \pi^1_y - \pi^1_z) - (\mu+\sigma)\pi^1_{h_2}, \tag{8.35}$$

$$\frac{d\pi^1_y}{dt} = \eta\pi^0_y + \sigma\pi^1_{h_1} - \mu\pi^1_y, \tag{8.36}$$

$$\frac{d\pi^1_z}{dt} = \eta\pi^0_z + \sigma\alpha\pi^1_{h_2} - \mu\pi^1_z, \tag{8.37}$$

where $\pi^i_j \geq 0$, $\sum_j \pi^0_j + \sum_j \pi^1_j = 1$ $(j = x, x_1, h_1, h_2, y, z)$ and $\underline{f}_0$, $\underline{f}_1$ are given by $\underline{f}_i = \lambda_{iF}\overline{s}_{i0}\frac{\overline{\psi}_0}{\pi^0}\left(\alpha_{hF}(\pi^0_{h_1} + \pi^0_{h_2}) + \alpha_{yF}\pi^0_y\right) + \lambda_{iF}\overline{s}_{i1}\frac{\overline{\psi}_1}{\pi^1}\left(\alpha_{hF}(\pi^1_{h_1} + \pi^1_{h_2}) + \alpha_{yF}\pi^1_y\right)$. Note that since the cleaning of filters prior to use is not mentioned in the published literature, $\underline{f}_i$ does not contain a term that accounts for the cleaning of filters prior to use.

In Chapter 6 we were able to use analytical techniques to derive an expression for R_0 and examine the existence and uniqueness of equilibrium solutions as well as the global stability of the DFE when $R_0 \leq 1$. It is possible to modify the proofs presented in Chapter 6 to obtain similar results for this model, however the expressions are more complicated. For example, in the derivation of the basic reproductive number the expression for κ_{00} given by (6.38) is replaced by

$$\begin{aligned}
&\frac{\lambda_0 s_{00}(1-\phi)\psi^*_0}{(\mu+\sigma+\eta)}\left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{(\mu+\eta)}\right] \\
&+ \lambda_0 s_{01}(1-\phi)\psi^*_1\frac{\pi^{0^*}}{\pi^{1^*}}\frac{\eta}{(\mu+\sigma+\eta)}\left[\frac{\alpha_h}{\mu+\sigma} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\sigma)} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\right] \\
&+ \frac{\lambda_{0F}\overline{s}_{00}\overline{\psi}^*_0}{(\mu+\sigma+\eta)}\left[\alpha_{hF} + \frac{\sigma(1-\delta)\alpha_{yF}}{(\mu+\eta)}\right] \\
&+ \lambda_{0F}\overline{s}_{01}\overline{\psi}^*_1\frac{\pi^{0^*}}{\pi^{1^*}}\frac{\eta}{(\mu+\sigma+\eta)}\left[\frac{\alpha_{hF}}{\mu+\sigma} + \frac{\sigma(1-\delta)\alpha_{yF}}{\mu(\mu+\sigma)} + \frac{\sigma(1-\delta)\alpha_{yF}}{\mu(\mu+\eta)}\right].
\end{aligned}$$

Since our main interest in this chapter is to estimate the potential risk of HCV transmission through the sharing of contaminated filters, we will focus on numerical simulation results rather than presenting a detailed mathematical analysis of this model.

8.3 Parameter estimates relating to filter sharing

Tables 8.1 and 8.2 show the baseline parameter estimates used in our simulations. Since we have already discussed the parameter estimates in Table 8.1 (see Section 7.1) we do not discuss them here. Instead we will discuss the parameter estimates that relate to filter sharing (Table 8.2).

8.3.1 Fraction of filters that are borrowed within groups $(\overline{s}_{00}, \overline{s}_{11})$ and across groups $(\overline{s}_{01}, \overline{s}_{10})$

As with the sharing of needles and syringes, there is no data available to allow us to determine the proportion of filter sharing that goes on within groups or across groups. When dealing with needles and syringes we assumed that IDUs prefer to borrow needles and syringes from IDUs in the same experience group (Subsection 7.1.7). We make a similar assumption here and assume that IDUs prefer to borrow filters from IDUs in the same group. We also have to ensure that condition (8.25) is satisfied. Hence we assume that $\overline{s}_{00} = 0.6667$, $\overline{s}_{01} = 0.3333$, $\overline{s}_{10} = 0.099$ and $\overline{s}_{11} = 0.901$.

8.3.2 Average working life of a filter $(365.25/\tau_f)$

Filters are used by IDUs to remove large, insoluble particles from the drug solution prior to injecting (Taylor *et al.* 2004). After injecting, it is common for IDUs to keep their filters for re-use at a later date. This allows IDUs to extract any remaining drug particles, especially when heroin, money or drug dealers are in short supply (Scott 2008). Since IDUs have been known to use cigarette butts, nappy linings, cotton swabs, female sanitary products and duvets as filters (Scott 2008), there is no accurate way to determine the working life of a filter. Unlike needles and syringes, filters do not get blocked or blunt and so it is reasonable to assume that the working life of a filter will be greater than the working life of a needle and syringe. With no other information available to us, we estimate that the working life of a filter is 6.52 days (double the working life of a needle and syringe).

Parameter	Estimate	Source	Notes
ϕ	0.255	Unpublished data HPS (1990-1993)	Observed data on Glasgow IDUs during 1990-1993
α_y	2.5%	Hutchinson, Bird *et al.* (2006)	Assumption based on observed data on HCV transmission through needle stick injury
α_h	6.75%	Conservative estimate	Estimate is 2.7 $\times\alpha_y$ based on Vickerman *et al.* (2007) model fits
$1/\sigma$	0.5 years	Vickerman *et al.* (2007, 2009)	Observed data from studies on acute HCV
α	0.25	Conservative estimate	Limited data available
δ	0.26	Micallef *et al.* (2006)	Review of longitudinal studies during 1980-2003
$1/\eta$	5 years		Assumption based on surveillance reports of IDUs
$1/\mu$	10.002 years	Calculated estimate	Based on assumed equilibrium proportion of naive IDUs and time since onset of injection
π^0	0.3333†	Unpublished data HPS (2008-2009)	Based on observed data of Glasgow IDUs during 2008-2009
π^1	0.6667†	Unpublished data HPS (2008-2009)	Based on observed data of Glasgow IDUs during 2008-2009
λ_0	1.96 per IDU per year	Unpublished data HPS (2008-2009)	Observed data on Glasgow IDUs during 2008-2009
λ_1	2.56 per IDU per year	Unpublished data HPS (2008-2009)	Observed data on Glasgow IDUs during 2008-2009
$365.25/\tau$	3.26 days	Hay *et al.* (2009); ISD Scotland (2010)	Based on the estimated number of Glasgow IDUs during 2008 and observed data on needle and syringe provision in Glasgow during 2008-2009
s_{00}	0.6667	Conservative estimate	No data available
s_{01}	0.3333	Conservative estimate	No data available
s_{10}	0.1276	Conservative estimate	No data available
s_{11}	0.8724	Conservative estimate	No data available

†assumed to be at equilibrium

Table 8.1: Table of baseline parameter estimates.

Parameter	Estimate	Source	Notes
λ_{0F}	53.28 per IDU per year	Unpublished data HPS (2004)	Observed data on Glasgow IDUs during 2004
λ_{1F}	89.63 per IDU per year	Unpublished data HPS (2004)	Observed data on Glasgow IDUs during 2004
$365.25/\tau_f$	6.52 days	Conservative estimate	No data available
$\overline{s}_{00}$	0.6667	Conservative estimate	No data available
$\overline{s}_{01}$	0.3333	Conservative estimate	No data available
$\overline{s}_{10}$	0.099	Conservative estimate	No data available
$\overline{s}_{11}$	0.901	Conservative estimate	No data available

Table 8.2: Table of parameter estimates that relate to filter sharing.

8.3.3 Filter sharing rate for naive (λ_{0F}) and experienced IDUs (λ_{1F})

From a survey of 564 current IDUs in Glasgow in 2004 (more recent surveys do not quantify the frequency of paraphernalia sharing in the period prior to interview), we were able to identify 142 naive IDUs (25.2%) and 422 experienced IDUs (74.8%). We examined the frequency of filter sharing for each group in the one month period prior to interview and estimated that there were 7,566 filter sharing events per year for the 142 naive IDUs and 37,824 filter sharing events per year for the 422 experienced IDUs. Therefore, the average filter sharing rate for naive IDUs (λ_{0F}) is 53.28 sharing events per IDU per year and the average filter sharing rate for experienced IDUs (λ_{1F}) is 89.63 sharing events per IDU per year.

8.4 Simulation results for filter sharing model

Using the baseline set of parameter estimates given in Tables 8.1 and 8.2 as well as the numerical simulation package Berkeley Madonna version 8.3.11 (Macey *et al.* 2000) we simulate the behaviour of this extended model over a period of 70 years. Our aim is to determine the transmission probability of acute and chronic HCV through filter sharing by finding the transmission probabilities that give us an endemic HCV prevalence which lies within the 95% CI for HCV prevalence among all Glasgow IDUs (including naive and experienced IDUs) during 2008-2009. We assume that IDUs do not under-report their needle and syringe sharing and hence the sharing of filters is the only possible extra source of transmission.

In estimating the transmission probabilities of acute (α_{hF}) and chronic (α_{yF}) HCV through filter sharing, we maintain the assumption that acute HCV will be 2.7 times more transmissible than chronic HCV because of the highly infectious six to eight week period immediately following infection. Hence, $\alpha_{hF} = 2.7\alpha_{yF}$ and we can concentrate on estimating a single transmission probability rather than trying to estimate two different transmission probabilities. Figure 8.1 shows a parameter plot of α_{yF} versus HCV prevalence among Glasgow IDUs. From this figure we estimate that in order to achieve an endemic HCV prevalence between 67% and 73% we require α_{yF}, the transmission probability of chronic HCV

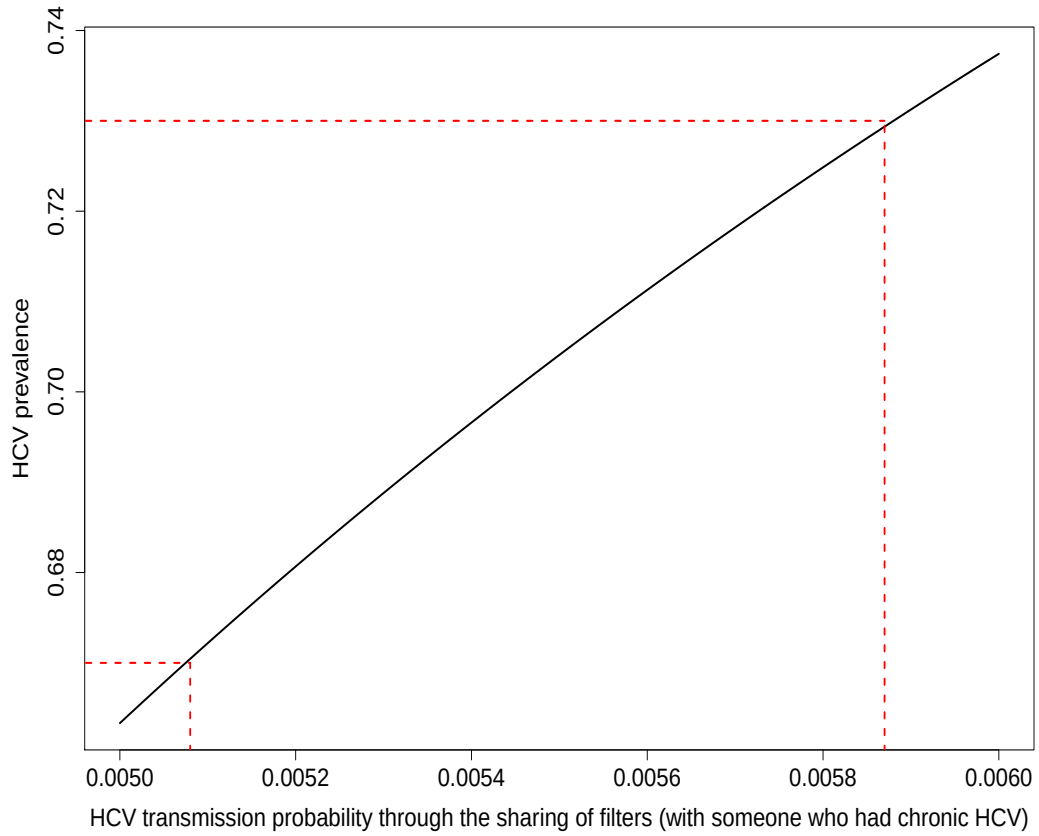

Figure 8.1: Parameter plot showing the values of α_{yF} required to achieve an endemic HCV prevalence of 67-73%.

through filters, to be between 0.508% and 0.587%. The transmission probability for chronic HCV through the sharing of needles and syringes is between four and five times greater than these estimates ($\alpha_y = 2.5\%$). These estimates imply that the transmission probability of acute HCV through filters is between 1.37% and 1.58%.

However, if we use these transmission probabilities to examine the prevalence of naive and experienced IDUs we see that our naive and experienced HCV prevalences do not fall within the 95% CIs for observed HCV prevalence (Figure 8.2). In fact, we under-estimate HCV prevalence among naive IDUs and over-estimate HCV prevalence among experienced IDUs. This suggests that filter sharing may not be the only cause of our poor model fit. Since these results suggest that there

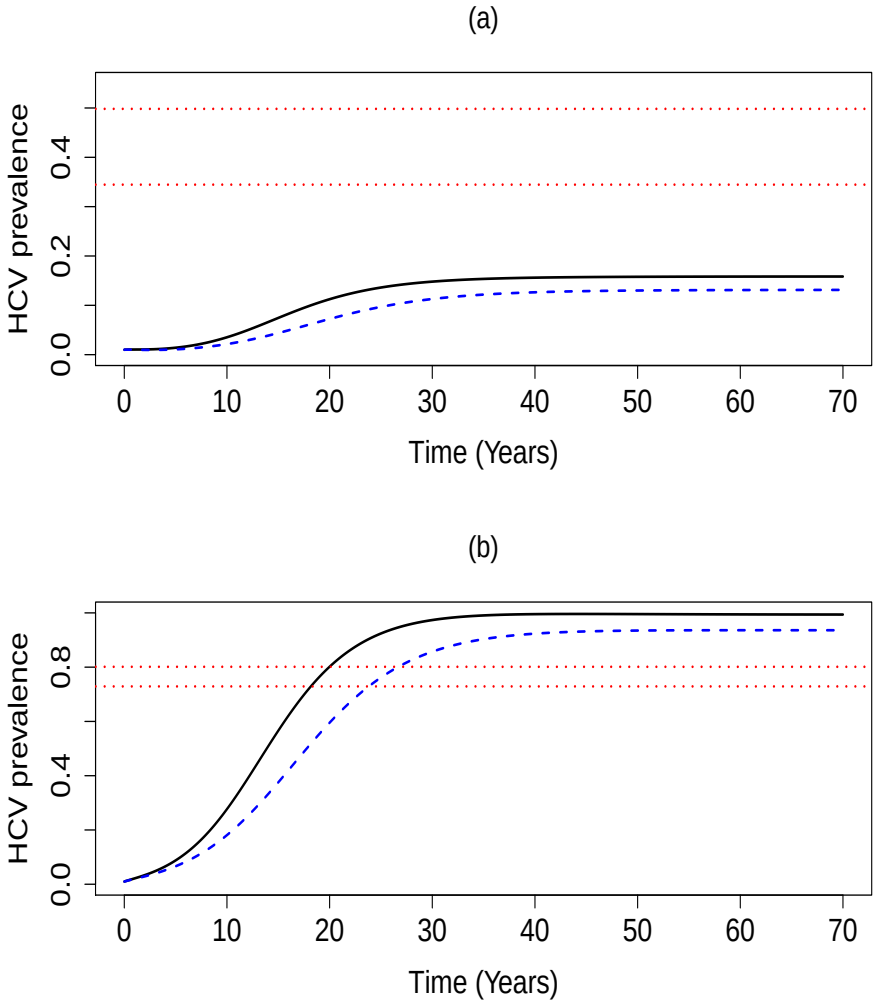

Figure 8.2: HCV prevalence for (a) naive IDUs and (b) experienced IDUs when $(\alpha_{hF}, \alpha_{yF}) = (0.0137, 0.00508)$ (solid black lines) and $(\alpha_{hF}, \alpha_{yF}) = (0.0158, 0.00587)$ (dashed blue lines). The 95% CIs for the observed HCV prevalence from a survey of naive IDUs (34.5-49.9%) and experienced IDUs (72.9-80.1%) are shown in red.

may be a risk of HCV infection through the sharing of filters, it makes sense to extend our model to incorporate some of the other paraphernalia that IDUs share. Therefore, we now examine the effects of introducing both filter sharing and cooker or spoon sharing.

8.5 Risk associated with filter and cooker or spoon sharing assuming reported needle and syringe sharing rates are correct

We now investigate the risk associated with filter and cooker or spoon sharing when we assume that IDUs do not under-report their needle and syringe sharing. Note that, for convenience, we now write filter and cooker sharing rather than filter and cooker or spoon sharing. The model structure and governing equations remain unchanged from our previous discussions, however, the parameters that relate to the sharing of filters have been modified to incorporate both filter and cooker sharing. Let λ_{0F}, λ_{1F} respectively denote the average filter and cooker sharing rate for naive and experienced IDUs, $\overline{s}_{jk}$ denote the fraction of filters and cookers that IDUs in group j borrow from IDUs in group k and α_{hF}, α_{yF} respectively denote the transmission probability of acute and chronic HCV through the sharing of filters and cookers.

8.5.1 Parameter estimates relating to filter and cooker sharing

Table 8.3 shows the baseline parameter estimates that relate to the sharing of filters and cookers. The other behavioural and biological parameter estimates needed for our numerical simulations remain unchanged from those summarised in Table 8.1.

8.5.2 Fraction of filters and cookers that are borrowed within groups $(\overline{s}_{00}, \overline{s}_{11})$ and across groups $(\overline{s}_{01}, \overline{s}_{10})$

As previously discussed, there is no data available to allow us to determine the proportion of filter and cooker sharing that goes on within groups or across groups. When dealing with needles and syringes we assumed that IDUs prefer to borrow needles and syringes from IDUs in the same experience group (Subsection 7.1.7). We make a similar assumption here and assume that IDUs prefer to borrow filters and cookers from IDUs in the same group. We also have to ensure that condition

Parameter	Estimate	Source	Notes
λ_{0F}	118.22 per IDU per year	Unpublished data HPS (2004)	Observed data on Glasgow IDUs during 2004
λ_{1F}	183.71 per IDU per year	Unpublished data HPS (2004)	Observed data on Glasgow IDUs during 2004
$365.25/\tau_f$	6.52 days	Conservative estimate	No data available
$\overline{s}_{00}$	0.6667	Conservative estimate	No data available
$\overline{s}_{01}$	0.3333	Conservative estimate	No data available
$\overline{s}_{10}$	0.1072	Conservative estimate	No data available
$\overline{s}_{11}$	0.8928	Conservative estimate	No data available

Table 8.3: Table of parameter estimates that relate to filter and cooker sharing.

(8.25) is satisfied. Hence we assume that $\overline{s}_{00} = 0.6667$, $\overline{s}_{01} = 0.3333$, $\overline{s}_{10} = 0.1072$ and $\overline{s}_{11} = 0.8928$.

8.5.3 Average working life of a filter and cooker ($365.25/\tau_f$)

There is no accurate way to determine the working life of a filter or cooker. Unlike needles and syringes, filters and cookers do not get blocked or blunt and so it is reasonable to assume that the working life of filters and cookers will be greater than the working life of a needle and syringe. With no other information available to us, we continue to estimate that the working life of both filters and cookers is 6.52 days (double the working life of a needle and syringe).

8.5.4 Filter and cooker sharing rate for naive (λ_{0F}) and experienced IDUs (λ_{1F})

From a survey of 564 current IDUs in Glasgow in 2004 (more recent surveys do not quantify the frequency of paraphernalia sharing in the period prior to interview), we were able to identify 142 naive IDUs (25.2%) and 422 experienced IDUs (74.8%). We examined the frequency of filter and cooker sharing for each group in the one month period prior to interview and estimated that there were 16,787 filter and cooker sharing events per year for the 142 naive IDUs and 77,525 filter and cooker sharing events per year for the 422 experienced IDUs. Therefore, the average filter and cooker sharing rate for naive IDUs (λ_{0F}) is 118.22 sharing events per IDU per year and the average filter and cooker sharing rate for experienced IDUs (λ_{1F}) is 183.71 sharing events per IDU per year.

8.6 Simulation results for filter and cooker sharing model

Using the baseline set of parameter estimates given in Tables 8.2 and 8.3 and the numerical simulation package Berkeley Madonna version 8.3.11 (Macey *et al.* 2000) we simulate the behaviour of this extended model over a period of 70 years. As with our previous simulations, our aim is to determine the transmission probability of acute and chronic HCV through filter and cooker sharing by finding

the transmission probabilities that give us an endemic HCV prevalence which lies within the 95% CI for HCV prevalence among all Glasgow IDUs (including naive and experienced IDUs) during 2009-2009.

8.6.1 Risk associated with filter and cooker sharing assuming reported needle and syringe sharing rates are correct

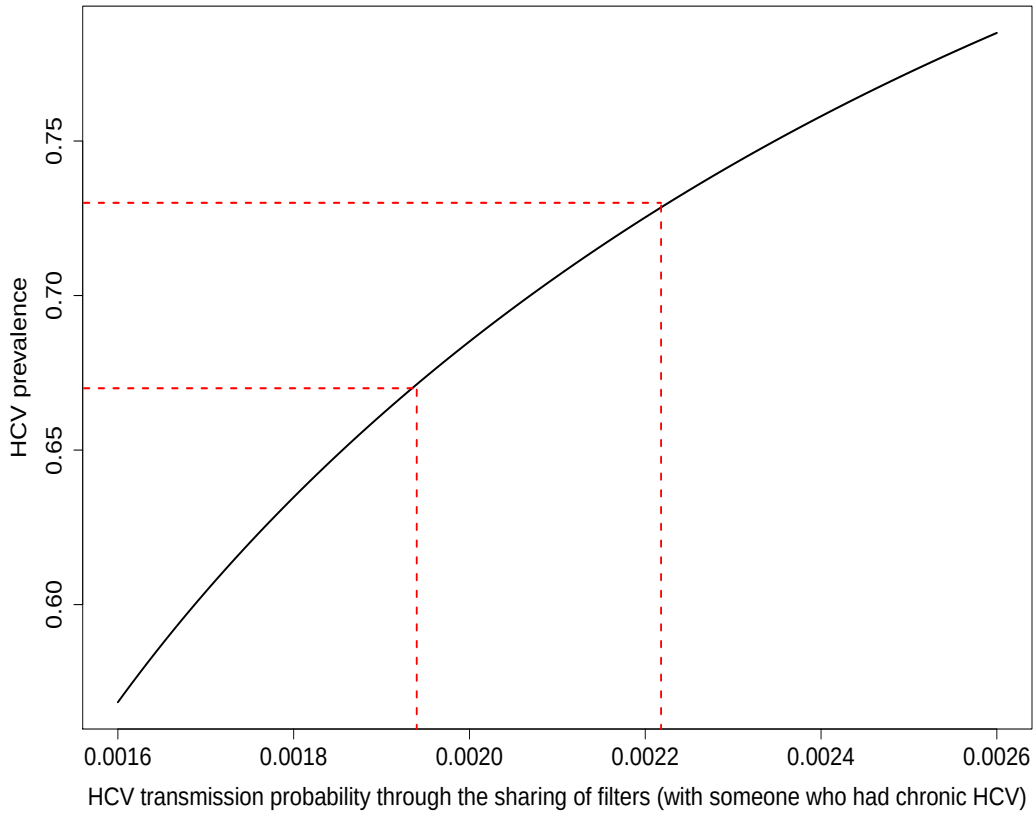

Figure 8.3: Parameter plot showing the values of α_{yF} required to achieve an endemic HCV prevalence of 67-73%.

We maintain the assumption that acute HCV will be 2.7 times more transmissible than chronic HCV because of the highly infectious six to eight week period immediately following infection. Hence, $\alpha_{hF} = 2.7\alpha_{yF}$ and we can concentrate on

estimating a single transmission probability rather than trying to estimate two different transmission probabilities. Figure 8.3 shows a parameter plot of α_{yF} versus HCV prevalence among Glasgow IDUs. From this figure we estimate that in order to achieve an endemic HCV prevalence between 67% and 73% we require α_{yF}, the transmission probability of chronic HCV through filters and cookers, to be between 0.194% and 0.221%. Note that the transmission probability for chronic HCV through the sharing of needles and syringes is approximately 12 times greater than these estimates ($\alpha_y = 2.5\%$). These estimates imply that the transmission probability of acute HCV through filters and cookers is between 0.52% and 0.60%.

However, if we again use these transmission probabilities to examine the prevalence of naive and experienced IDUs we see that our naive and experienced HCV prevalences do not fall within the 95% CIs for observed HCV prevalence (Figure 8.4). As in our earlier simulations (conducted in Section 8.4), we under-estimate HCV prevalence among naive IDUs and over-estimate HCV prevalence among experienced IDUs.

8.6.2 Evaluating the impact that the working life of cookers and filters ($365.25/\tau_f$) has on our transmission probability estimates

In our simulations we assume what we feel is a reasonable estimate for the working life of filters and cookers. In order to see how sensitive our estimate for the transmission probability related to acute and chronic HCV through the sharing of these items is to our estimate for the working life (6.52 days at baseline), we use three different working life estimates: $\tau_f = 3.26$ days (the same working life as a needle and syringe), $\tau_f = 6.52$ days (our baseline estimate) and $\tau_f = 9.78$ days (three times the working life of a needle and syringe). Note that we assume that IDUs do not under-report their needle and syringe sharing and that all other parameter estimates are fixed at the baseline values described in Tables 8.1 and 8.3. In addition, we continue to assume that acute HCV will be 2.7 times more transmissible than chronic HCV because of the highly infectious six to eight week period immediately following infection. Hence, $\alpha_{hF} = 2.7\alpha_{yF}$. The result of our investigations are summarised in Table 8.4.

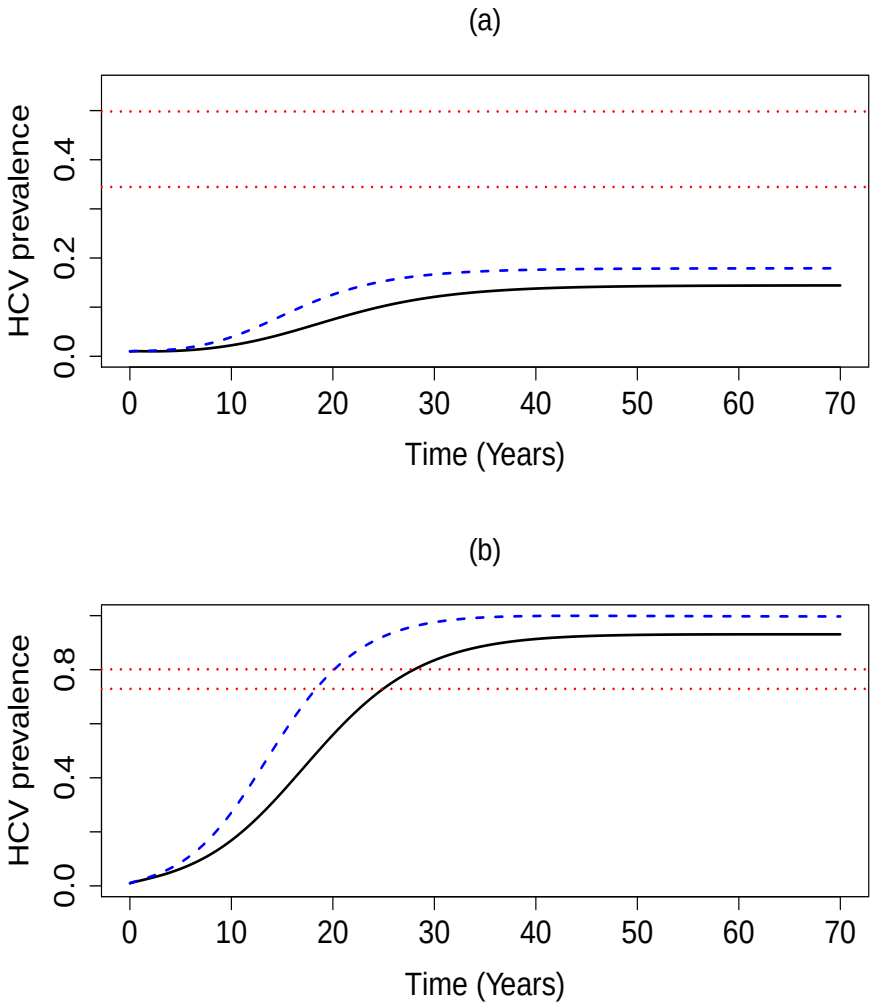

Figure 8.4: HCV prevalence for (a) naive IDUs and (b) experienced IDUs when $(\alpha_{hF}, \alpha_{yF}) = (0.0052, 0.00194)$ (solid black lines) and $(\alpha_{hF}, \alpha_{yF}) = (0.0060, 0.00221)$ (dashed blue lines). The 95% CIs for the observed HCV prevalence from a survey of naive IDUs (34.5-49.9%) and experienced IDUs (72.9-80.1%) are shown in red.

Working life of filters and cookers	α_{hF}	α_{yF}
3.26 days	0.00675	0.00250
6.52 days	0.00564	0.00209
9.78 days	0.00529	0.00196

Table 8.4: Acute and chronic HCV transmission probabilities for different estimates for the working life of cookers and filters.

From Table 8.4 we see that changes in the working life do not result in large changes in our acute and chronic HCV transmission probability estimates. Decreasing the working life of filters and cookers to match the working life of needles and syringes increased our estimate for the transmission probability of chronic HCV by only 0.041%. Similarly, increasing the working life of cookers and filters reduced the chronic HCV transmission probability estimate by 0.013%. These results suggest that the model is not sensitive to τ_f.

We have now examined the risk associated with the sharing of filters and cookers. Since it is possible to detect HCV RNA in water samples (Crofts *et al.* 2000) we now extend the model again in order to allow for HCV transmission to occur through the sharing of filters, cookers and water.

8.7 Risk associated with filter, cooker and water sharing assuming reported needle and syringe sharing rates are correct

We now investigate the risk associated with filter, cooker and water sharing when again assuming that IDUs do not under-report their needle and syringe sharing. Note that, for convenience, we shall now write paraphernalia sharing rather than filter, cooker and water sharing. The model structure and governing equations remain unchanged from our previous discussions, however, we have to modify the parameter estimates presented in Table 8.3 to incorporate the sharing of water. Let λ_{0F}, λ_{1F} respectively denote the average paraphernalia sharing rate for naive and experienced IDUs, $\overline{s}_{jk}$ denote the fraction of paraphernalia that IDUs in group j borrow from IDUs in group k and α_{hF}, α_{yF} respectively denote the transmission probability of acute and chronic HCV through paraphernalia sharing.

8.7.1 Parameter estimates relating to paraphernalia sharing

Table 8.5 shows the baseline parameter estimates that relate to the sharing of injecting paraphernalia. The other behavioural and biological parameter estimates

needed for our numerical simulations are still unchanged from those summarised in Table 8.1.

8.7.2 Fraction of paraphernalia that are borrowed within groups $(\overline{s}_{00}, \overline{s}_{11})$ and across groups $(\overline{s}_{01}, \overline{s}_{10})$

As previously discussed, there is no data available to allow us to determine the proportion of paraphernalia that goes on within groups or across groups. Previous estimates for these parameters have assumed that IDUs prefer to borrow items from IDUs in the same experience group (Subsections 7.1.7, 8.3.1 and 8.5.2). We make a similar assumption here and assume that IDUs prefer to borrow paraphernalia from IDUs in the same group. We also have to ensure that condition (8.25) is satisfied. Hence we assume that $\overline{s}_{00} = 0.6667$, $\overline{s}_{01} = 0.3333$, $\overline{s}_{10} = 0.1123$ and $\overline{s}_{11} = 0.8877$.

8.7.3 Average working life of paraphernalia $(365.25/\tau_f)$

There is no accurate way to determine the working life of injecting paraphernalia. Unlike needles and syringes, other drug preparation items do not get blocked or blunt and so it is reasonable to assume that the working life of injecting paraphernalia will be greater than the working life of a needle and syringe. With no other information available to us, we continue to estimate that the working life of injecting paraphernalia is 6.52 days (double the working life of a needle and syringe).

8.7.4 Paraphernalia sharing rate for naive (λ_{0F}) and experienced IDUs (λ_{1F})

From a survey of 564 current IDUs in Glasgow in 2004 (more recent surveys do not quantify the frequency of paraphernalia sharing in the period prior to interview), we were able to identify 142 naive IDUs (25.2%) and 422 experienced IDUs (74.8%). We examined the frequency of paraphernalia sharing for each group in the one month period prior to interview and estimated that there were 27,071 paraphernalia sharing events per year for the 142 naive IDUs and 119,327 paraphernalia sharing events per year for the 422 experienced IDUs. Therefore, the

Parameter	Estimate	Source	Notes
λ_{0F}	190.64 per IDU per year	Unpublished data HPS (2004)	Observed data on Glasgow IDUs during 2004
λ_{1F}	282.765 per IDU per year	Unpublished data HPS (2004)	Observed data on Glasgow IDUs during 2004
$365.25/\tau_f$	6.52 days	Conservative estimate	No data
$\overline{s}_{00}$	0.6667	Conservative estimate	No data available
$\overline{s}_{01}$	0.3333	Conservative estimate	No data available
$\overline{s}_{10}$	0.1123	Conservative estimate	No data available
$\overline{s}_{11}$	0.8877	Conservative estimate	No data available

Table 8.5: Table of parameter estimates that relate to paraphernalia sharing.

average paraphernalia sharing rate for naive IDUs (λ_{0F}) is 190.64 sharing events per IDU per year and the average paraphernalia sharing rate for experienced IDUs (λ_{1F}) is 282.765 sharing events per IDU per year.

8.8 Simulation results for paraphernalia sharing model

Using the baseline set of parameter estimates given in Tables 8.2 and 8.5 and the numerical simulation package Berkeley Madonna version 8.3.11 (Macey *et al.* 2000) we simulate the behaviour of this extended model over a period of 70 years. As with our previous simulations, our aim is to determine the transmission probability of acute and chronic HCV through paraphernalia sharing by finding the transmission probabilities that give us an endemic HCV prevalence which lies within the 95% CI for HCV prevalence among all Glasgow IDUs (including naive and experienced IDUs) during 2008-2009.

We continue to assume that acute HCV will be 2.7 times more transmissible than chronic HCV because of the highly infectious six to eight week period immediately following infection. Hence, $\alpha_{hF} = 2.7\alpha_{yF}$ and we can concentrate on estimating a single transmission probability rather than trying to estimate two different transmission probabilities. Figure 8.5 shows a parameter plot of α_{yF} versus HCV prevalence among Glasgow IDUs. From this figure we estimate that in order to achieve an endemic HCV prevalence between 67% and 73% we require α_{yF}, the transmission probability of chronic HCV through the sharing of paraphernalia, to be between 0.114% and 0.130%. Note that the transmission probability for chronic HCV through the sharing of needles and syringes is approximately 22 times greater than these estimates ($\alpha_y = 2.5\%$). These estimates imply that the transmission probability of acute HCV through the sharing of paraphernalia is between 0.308% and 0.351%.

However, if we again use these transmission probabilities to examine the prevalence of naive and experienced IDUs we see that our naive and experienced HCV prevalences do not fall within the 95% CIs for observed HCV prevalence (Figure 8.6). As in our earlier simulations (conducted in Subsections 8.4.1 and 8.6.1), we under-estimate the prevalence of HCV amongst naive IDUs and over-estimate

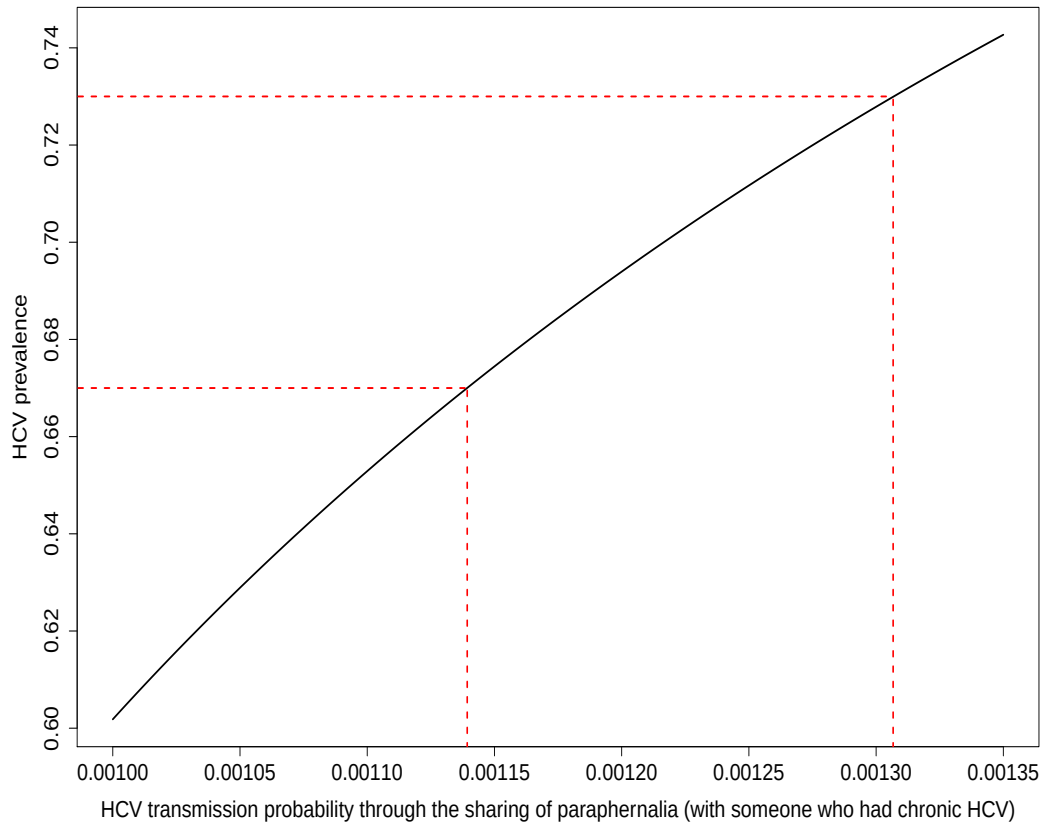

Figure 8.5: Parameter plot showing the values of α_{yF} required to achieve an endemic HCV prevalence of 67-73%.

the prevalence of HCV amongst experienced IDUs.

8.9 Conclusions and discussion

The risk of HCV infection through the sharing of injecting paraphernalia (such as cookers, filters and water) has not received the attention that the risk associated with needle and syringe sharing has. Recent evidence has suggested that the sharing of injecting paraphernalia equipment may contribute to the spread of HCV amongst IDUs (Crofts *et al.* 2000; Hagan *et al.* 2001; Mathei *et al.* 2006; De *et al.* 2008). Given that IDUs are reporting high levels of injecting paraphernalia sharing (Koester 1996; Speed 1998; Gaskin *et al.* 2000; NESI 2010), it

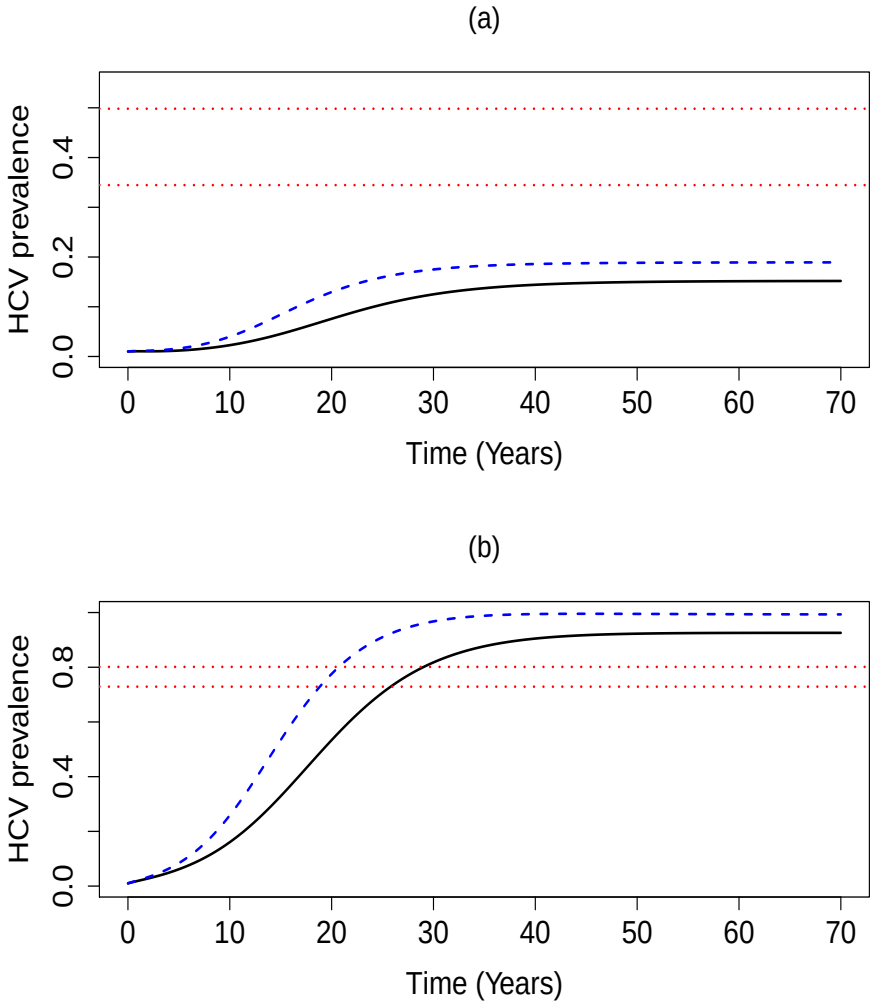

Figure 8.6: HCV prevalence for (a) naive IDUs and (b) experienced IDUs when $(\alpha_{hF}, \alpha_{yF}) = (0.00308, 0.00114)$ (solid black lines) and $(\alpha_{hF}, \alpha_{yF}) = (0.00351, 0.00130)$ (dashed blue lines). The 95% CIs for the observed HCV prevalence from a survey of naive IDUs (34.5-49.9%) and experienced IDUs (72.9-80.1%) are shown in red.

is important to quantify the role that the sharing of these items play in disease transmission.

In the previous chapter we assumed that an under-reporting of needle and syringe sharing rates caused our time since onset of injection model to underestimate HCV prevalence rates observed through surveys of IDUs. In this chapter we extended our time since onset of injection model in Chapter 6 to allow for HCV transmission through the sharing of paraphernalia. We first derived the governing equations for this extended version of the model. Then, using Berkeley Madonna version 8.3.11 (Macey *et al.* 2000) we estimated the probability of (acute and chronic) HCV transmission through (i) filter sharing, (ii) filter and cooker or spoon sharing and (iii) filter, cooker or spoon and water sharing. In all cases we assume that IDUs do not under-report their needle and syringe sharing and hence the sharing of other paraphernalia is the only possible extra source of transmission.

We first examined the case where the only extra source of transmission was from filter sharing. In this case we found that the probability of HCV transmission through filters was between 1.37% and 1.58% for acute and 0.508% and 0.587% for chronic HCV infection. We also found that despite obtaining Glasgow HCV prevalence estimates within the 95% CI for the observed prevalence of HCV amongst all current IDUs in Glasgow during 2008-2009, the prevalence estimates for naive and experienced IDUs were outside their 95% CIs.

We then used this model to examine the risks associated with filter and cooker sharing, again assuming that IDUs do not under-report their needle and syringe sharing. As expected, the average sharing rates for filters and cookers were higher than the estimates for filter sharing alone. Furthermore, this increase in sharing rates resulted in lower estimates for the transmission probability of acute and chronic HCV (0.52%-0.60% for acute HCV, 0.194%-0.221% for chronic HCV). Similar to our filter-only simulations we found that despite obtaining HCV prevalence estimates that were within the 95% CI for the observed prevalence of HCV amongst all current Glasgow IDUs during 2008-2009, the model does not reproduce the observed prevalence of HCV amongst naive and experienced IDUs.

Finally we extended this model further to allow for transmission to occur through the sharing of all injecting paraphernalia. Here the term paraphernalia referred to filters, cookers and water. Again we saw an increase in the average

sharing frequency when water was incorporated and a reduction in the transmission probability of acute and chronic HCV infection. In line with our earlier simulations we found that the model was unable to reproduce the observed prevalence of HCV amongst naive and experienced IDUs in Glasgow during 2008-2009, despite providing prevalence estimates that were within the 95% CI for the observed prevalence of HCV amongst current IDUs in Glasgow for the same period.

This modelling exercise suggests that the transmission probability of HCV though all injecting paraphernalia appears to be between 0.114% and 0.130% for chronic HCV and 0.308% and 0.351% for acute HCV. However, it is difficult to determine if this risk is a viable method for HCV transmission. Given that IDUs are sharing paraphernalia it is imperative that researchers determine what constitutes a viable method of HCV transmission so that preventative measures may be taken.

In our simulations we have assumed that the self-reported needle and syringe sharing rates are correct. However, it is possible that IDUs will under-report their needle and syringe sharing risk behaviour (Greenfield *et al.* 1995; des Jarlais *et al.* 1999). This would mean that we would need to increase the amount of needle and syringe sharing in our simulations which would in turn reduce our estimate for the transmission probability of acute and chronic HCV infection through the sharing of paraphernalia. Therefore, it is important that we understand to what extent IDUs under-report their needle and syringe sharing so that we can gain more accurate estimates of the risk of HCV infection through the sharing of injecting paraphernalia.

For our model, we needed information on the working life of filters, cookers and water. This information is not easy to collect given these items can be readily obtained by IDUs through sources external to services (Scott 2008). If the working life of paraphernalia is longer that assumed here (that is 6.52 days, twice that assumed for needles and syringes), then the risk of infection associated with the sharing of paraphernalia would decrease from our estimate. Simulations were conducted to see how sensitive our model predictions were to this working life estimate. We found that simulations conducted with a working life of either 3.26 days (equal to that assumed for needles and syringes) or 9.78 (three times that assumed for needles and syringes) had little effect on our estimates for the risk of infection.

As with all modelling studies there are some limitations to our research. The deterministic nature of our model does not allow us to incorporate the random variability in needle and syringe sharing rates and paraphernalia sharing rates. That said, we do allow for a level of heterogeneity in these sharing rates by modelling the spread of HCV infection amongst two risk groups (naive and experienced) with different risk behaviours. It is reasonable to consider that the transmission probability of HCV through filters will be different from the transmission probabilities of HCV through cookers and water. Our simulations were unable to generate separate transmission probabilities for filters, cookers and waters. Therefore, we are unable to determine whether one particular item of equipment poses a greater risk than the others.

This concludes our investigation into the risk of HCV infection through the sharing of injecting paraphernalia and the work of our thesis. In the next chapter we shall summarise the work contained in this thesis and suggest some future work ideas.

Chapter 9

Summary and further work

HCV is a global epidemic affecting the health of millions of people worldwide. In resource-rich countries like the United Kingdom, IDUs are at the greatest risk of contracting the disease through high risk injecting behaviour such as the sharing of needles and syringes. Since IDUs are more at risk of contracting HCV than HIV, recent recommendations have focused on the prevention of HCV infection in this population. 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 IDU population. With this in mind, the work contained in this thesis focused on the spread of HCV amongst IDUs and in particular IDUs in Glasgow, given the wealth of epidemiological data available for this population. Our aim was to develop and analyse mathematical models that approximate the spread of HCV amongst IDUs and then use these models to determine the critical levels of needle and syringe sharing, needle cleaning, and needle turnover, below which HCV elimination can occur.

We began with a discussion of the biology and epidemiology of HCV infection. We then discussed some of the techniques and concepts used in the mathematical modelling of infectious diseases and, with the aid of some examples, we highlighted how these models could be used to evaluate the effectiveness of intervention measures and help understand how an infectious disease spreads. We next reviewed some mathematical models for the spread of HIV amongst IDUs. The techniques used to develop and analyse these models can be used to help in the development of models for the spread of HCV amongst IDUs. After discussing the techniques

used in these models and some of their results we reviewed mathematical models for the spread of HCV amongst IDUs through the sharing of needles and syringes. This review was conducted during the early stages of this PhD and since the mathematical modelling of HCV amongst IDUs is an active research area, it makes sense to update this review and discuss any new research in this area.

9.1 Recent research on the mathematical modelling of HCV amongst IDUs through the sharing of needles and syringes

Using the search terms that were used in Section 1.12 a literature search of PUBMED (July 2009 to September 2011), EMBASE (July 2009 to September 2011) and Web of Knowledge (July 2009 to September 2011) was performed to identify English language, peer reviewed articles on the mathematical modelling of HCV amongst IDUs. A search of titles, abstracts and keywords was again performed and papers were selected following the screening of abstracts. We identified two mathematical modelling papers, which examined the spread of HCV amongst IDUs through the sharing of needles and syringes. Both of these models were used to evaluate the potential effect of antiviral therapy on the HCV burden amongst IDUs.

Both Martin, Vickerman, Foster *et. al* (2011) and Martin, Vickerman, and Hickman (2011) use similar deterministic compartmental models to model the transmission of HCV amongst IDUs. These models incorporated the treatment of active IDUs with antiviral therapy, which was assumed to achieve SVR in 62.5% of cases.

9.1.1 The model of Martin, Vickerman, Foster *et al.*

First of all we shall discuss the work of Martin, Vickerman, Foster *et. al* (2011).

This modelling work was used to project the potential impact of antiviral therapy on the prevalence of HCV amongst active IDUs, while allowing for re-infection. This model separated an IDU population into five groups by HCV infection status. IDUs could be susceptible to infection (susceptible IDUs in-

cluded those who had spontaneously resolved a previous infection and had not become immune to re-infection), chronically infected but naive to treatment or re-infected with HCV, chronically infected and failed treatment, immune to re-infection and currently in treatment. At baseline, the model assumed that there was no immunity to re-infection with HCV and that IDUs who failed to achieve SVR were not re-treated. The model assumed that infected IDUs who are naive to treatment or IDUs who have been re-infected with HCV are recruited to treatment at a constant rate of ϕ per 1,000 IDUs per year. It was assumed that IDUs could leave the population at any stage, due to death or cessation of injecting, at a constant per capita rate and that those who were undergoing treatment were uninfectious.

The authors used data from treatment guidelines and published literature to parameterise the model and assumed that the infection, clearance and treatment success rates for those who had cleared a previous infection was the same as the infection, clearance and treatment success rates for those who had not previously been infected. The treatment of IDUs commenced when the model had reached an endemic equilibrium prevalence. Numerical simulations were used to investigate the effect of increasing the treatment success rate from 62.5% to 80% or decreasing it to 45%. These different scenarios were used to mimic situations where there are different genotype distributions or a reduction in SVR due to non compliance with treatment.

Further analysis examined the effect of how re-treating those who failed to achieve SVR and the inclusion of immunity changed the model predictions. When including the re-treatment of IDUs, the authors assumed that the rate of treatment success was the same as the rate for those who were naive to treatment. Uncertainty analysis was performed using the latin hypercube method. This method sampled the parameter uncertainty space and allowed the authors to ascertain how the uncertainty in some parameters affected the projections for the baseline scenario.

Results

For an IDU population with a baseline equilibrium HCV prevalence of 20%, the authors found that applying treatment rates of 5, 10, 20 and 40 per 1,000 IDUs per year resulted in the prevalence of HCV decreasing by 15%, 30%, 62% and

72% respectively over a period of 10 years. However, increasing the baseline equilibrium HCV prevalence to 40% halved the projected decrease in prevalence over the same period. A baseline HCV prevalence of 60% would quarter the projected decreases over this timespan.

Further simulations showed how the projected impact could vary over time. A treatment programme which treats 10 per 1,000 IDUs per year in an IDU population with a baseline equilibrium HCV prevalence of 20% would see a 16% reduction in the prevalence of HCV within 5 years, a 30% reduction within 10 years and a 57% reduction after 20 years. In contrast, employing the same treatment programme in an IDU population with a baseline equilibrium HCV prevalence of 60% would see only a 9% reduction after 20 years.

The authors also found that a treatment programme which treats 5 per 1,000 IDUs per year can only reduce prevalence by more than 20% within 20 years if the baseline equilibrium prevalence of HCV is no more than 25%. To achieve the same impact in IDU populations where the endemic equilibrium prevalence of HCV is more than 60%, treatment programmes need to treat more than 20 per 1,000 IDUs per year.

Sensitivity analysis, based on a treatment programme which treats 20 per 1,000 IDUs per year, showed that the inclusion of immunity to HCV re-infection did not affect the projected impact of HCV antiviral treatment. In addition, the re-treatment of IDUs who fail to achieve SVR does not change the behaviour of the model unless the baseline equilibrium prevalence of HCV is less than 20% or less than 30% with a treatment programme which treats at least 20 per 1,000 IDUs per year.

9.1.2 The Martin, Vickerman and Hickman (2011) model

Next we shall discuss the model of Martin, Vickerman, and Hickman (2011).

In this modelling work the authors obtained analytical solutions for the level of treatment needed to eliminate or control HCV amongst an IDU population. The model examined the effect of two different treatment options on the prevalence of HCV amongst IDUs which allowed the authors to examine how changing the treatment delivery strategy affects the impact that treatment has on the prevalence of HCV. Option one assumed that a constant proportion of IDUs were

treated annually while option two assumed that a constant number of infected IDUs were treated annually. Option one is commonly used in infectious disease modelling and may be more reasonable since there are difficulties in finding, testing and recruiting IDUs to treatment. However, option two may reflect the initial stages of a treatment programme or one where there are budget constraints (Martin, Vickerman, and Hickman 2011).

This model allowed for four groups of IDUs: susceptible IDUs, IDUs who are currently in treatment, chronic IDUs (this class also includes the acutely infected IDUs who develop chronic infection), those who are undergoing treatment for HCV infection and those who are immune to HCV re-infection (some of those who have spontaneously resolved a previous infection, and those who become immune after achieving SVR). IDUs who fail to achieve SVR return to the infection compartment and can be retreated. The model assumed that a low proportion of IDUs who spontaneously clear a previous infection become immune to re-infection, however, the sensitivity of the model with respect to immunity was explored. It is assumed that IDUs who are undergoing treatment for HCV infection are not infectious (since HCV viral load drops substantially during the first few weeks of treatment). Furthermore, the probability that an IDU spontaneously clears an infection, develops immunity to HCV re-infection and achieves SVR following treatment are assumed to be the same for those previously uninfected with HCV and those who have been re-infected with HCV.

The authors used published literature on injecting drug use and HCV treatment to parameterise the model. Although this model did not explicitly model infections with different genotypes, it did incorporate a weighted average cure rate to allow for the differences in the treatment response rates. The authors assumed that 50% of cases would have HCV genotype one while the other 50% would have HCV genotypes two and three. Therefore, the authors assumed that the treatment response rates and treatment durations were an average of the response rates and duration for genotype one and genotypes two and three.

Results

For their numerical simulations, the authors initiated the treatment of IDUs once the model had reached an equilibrium HCV prevalence (time $t = 0$). Assuming a baseline endemic equilibrium HCV prevalence of 40% the numerical

simulations showed that increasing treatment rates results in greater reductions in HCV prevalence within a period of 10-20 years. The results showed that treating 2% of infected IDUs per year results in a 15% decrease in the prevalence of HCV in 20 years. However, increasing the treatment level to 4% of infected IDUs per year results in the prevalence of HCV decreasing by one third over the same period. Increasing the treatment level to 6% showed that the prevalence would be halved over the same time period. None of these treatment options achieved HCV elimination.

When the authors assumed that a fixed number of IDUs were treated annually they found that the model behaved differently. Their simulations used the same baseline prevalence of HCV and further assumed that the level of treatment was either 8, 16 or 24 per 1,000 IDUs per year. These rates were, at time $t = 0$, equivalent to treating 2%, 4% or 6% of infected IDUs. However, because the level of treatment remains constant, an increasing number of IDUs are treated as HCV prevalence decreases. Using this method, the authors found that a treatment programme which treats 16 per 1,000 IDUs per year will achieve HCV elimination within 60 years. Furthermore, increasing the level of treatment beyond this threshold resulted in a shorter time to HCV elimination.

The sensitivity of the critical threshold treatment level to the model parameters was examined and the authors found that the model was most sensitive to changes in injecting duration and infection risk. In addition, the authors found that immunity had little effect on the treatment threshold.

Limitations of this research

Both of these models have shown how the treatment of current IDUs can be used to prevent the spread of HCV and reduce the prevalence of HCV amongst active IDUs. In their discussion sections the authors mention several limitations in their modelling work. The authors assume that treatment for infection was sustained at the same rate, even if the prevalence of HCV in this population has decreased. Therefore, as prevalence of HCV decreases in the population, the proportion of infected IDUs recruited to treatment must increase. However, the difficulties in finding, testing and recruiting active IDUs to treatment programmes may result in a decrease in the level of treatment which would reduce the projected impact on the prevalence of HCV amongst the IDU population. Another point worth

mentioning is that the authors have assumed that IDUs who have spontaneously resolved an infection have the same probabilities of re-infection, recovery and immunity as those who have not previously been infected. It is possible that heterogeneities in risk behaviour during and following treatment may increase the risk of an IDU failing treatment or becoming re-infected. Such variations may result in the treatment programme failing to achieve the level of impact suggested by the models.

This completes our update on recent mathematical modelling work on the spread of HCV amongst IDUs through the sharing of needles and syringes. In the following section we shall summarise the main results from the thesis.

9.2 Summary of main results

The thesis started with a systematic review of the literature before proceeding to the main results.

9.2.1 Risk of HCV re-infection following spontaneous viral clearance in IDUs

In order to aid in the development of accurate HCV transmission models and to help inform studies of immune protection and vaccine development, a systematic review of the scientific literature was conducted. The rates of acute and chronic HCV infection between IDUs who had previously cleared infection and those not previously infected were compared and the evidence of HCV re-infection with either the same or a different genotype was examined. We found that the evidence relating to the risk of acute and chronic HCV in those previously infected with, but having cleared, HCV is limited. Furthermore, we found that IDUs who have previously cleared an HCV infection can be re-infected with either the same or a different HCV genotype. Our review found that comparable proportions of IDUs were found to be re-infected with either the same or a different HCV genotype, suggesting that the risk of re-infection is not influenced by a past HCV genotype infection. Therefore, we concluded that more research is needed among larger IDU cohorts over longer follow-up periods to accurately quantify the risks associated with HCV re-infection.

9.2.2 Using a simple mathematical model for the spread of HCV amongst IDUs

Our first model was a simple deterministic compartmental transmission model where we assumed that the IDU population was homogeneous in their needle and syringe sharing risk behaviour and time since onset of injection. In contrast to previous modelling work in this area our model explicitly modelled the number of needles and syringes by HCV infection status. After deriving the equations which governed the behaviour of the model as well as an expression for the basic reproductive number R_0, we conducted an extensive mathematical analysis of the model (Chapter 3). 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 the population, then the model tends towards a globally stable DFE where HCV has been eliminated in all IDUs and needles. If $R_0 > 1$ we found that HCV will persist in the population and for a realistic approximation to the basic model there is a locally stable endemic equilibrium. Furthermore, we found that if HCV is initially present in IDUs or needles and $R_0 > 1$, the model will tend towards the endemic equilibrium provided that certain conditions are satisfied.

Numerical simulations using this simple HCV transmission model, presented in Chapter 4, 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 IDUs and needles. Extensive simulations were conducted and these simulations confirmed our analytical results. We were able to determine analytically and through numerical simulation the critical values of needle and syringe sharing (λ), needle cleaning (ϕ) and needle turnover (τ) which resulted in $R_0 = 1$. We found that, provided all other parameters remain fixed, $\lambda \leq 54.67$ per year, $\phi \geq 0.74$ and $\tau \geq 562.37$ per year would result in eventual HCV elimination in all IDUs and needles. Further simulations showed that increasing the level of intervention past these critical levels results in a faster time to DFE.

9.2.3 Modelling the highly infectious acute stage of infection

Initial HCV infection may be followed by a short six to eight week period of high viraemia; a phenomenon similar to HIV. In our simple model we did not explicitly model this highly infectious phase. Instead we modelled a single acute stage with a single transmission probability which was an average of the high and low transmission probabilities. We therefore, extended our simple HCV transmission model to explicitly model the proportion of IDUs in the highly infectious acute stage of infection. We derived the governing system of differential equations and an expression for R_0. We examined two different ways of modelling this phase numerically, and in both cases we found that when this highly infectious phase was explicitly modelled there was an increased rate of HCV spread and a shorter time to endemic equilibrium. However, one method did not change the endemic equilibrium prevalence of HCV amongst Glasgow IDUs while the other resulted in a higher endemic equilibrium prevalence of HCV. These results lead us to conclude that more work must be done in understanding the existence of a highly infectious phase and how it should be modelled.

9.2.4 Using a time since onset of injection model for the spread of HCV amongst IDUs

Our next goal was to introduce more heterogeneity into our HCV transmission models. Therefore, we developed a deterministic mathematical model which, in addition to separating the population by their HCV infection status, also separated the population into two risk groups (naive and experienced) by their time since onset of injection. Each risk group had different injecting risk behaviours. We discussed the formulation of two models: one that explicitly modelled needles and syringes and one that modelled IDUs only. After showing that these models were equivalent we conducted a formal analysis of the IDU only model.

Although the complexity of the model limited our analysis, we showed that the behaviour of this model is also governed by R_0. We found that if $R_0 \leq 1$ and the disease is initially present in the population, then the system will tend toward the globally stable DFE where HCV has been eliminated in all IDUs and needles.

If $R_0 > 1$ we have shown that there is a unique endemic equilibrium. We then conducted a number of numerical simulations on this model and confirmed that it behaved in a similar way to the other HCV transmission models we had developed. Furthermore, we found that if data from recent community-wide surveys of IDUs in Glasgow were used for our parameter estimates the model predicted a marked decrease in the prevalence of HCV amongst IDUs. This decrease contradicted the estimated HCV prevalence amongst Glasgow IDUs. Therefore, we decided to examine possible explanations for this contradictory result.

9.2.5 Determining the extent of under-estimation in needle and syringe sharing rates amongst Glasgow IDUs

One possible explanation for the inability of our model to reproduce the observed HCV prevalence estimate was that IDUs under-report their needle and syringe sharing frequency. Therefore, we set out to determine to what extent IDUs in Glasgow under-report their needle and syringe sharing. We modified our time since onset of injection model to include terms that multiplied the estimated needle and syringe sharing rates for each risk group. These terms could then be used to increase the level of needle and syringe sharing for each risk group until the simulated endemic HCV prevalence estimate was within the 95% CI for the observed HCV prevalence amongst Glasgow IDUs. Assuming that both naive and experienced IDUs under-report their needle and syringe sharing by the same factor, our results suggested that the true needle and syringe sharing rates were somewhere between 24.8 and 28.2 times higher than are reported. While these results reproduced the observed prevalence of HCV amongst all IDUs in Glasgow, they did not replicate the observed prevalence of HCV amongst each individual risk group. Further simulations assumed that naive and experienced IDUs under-report their needle and syringe sharing by different factors. Our results suggested that naive IDUs were under-estimating their needle and syringe sharing by a factor of 34 and experienced IDUs were under-reporting their needle and syringe sharing by a factor of 16.

9.2.6 Risks associated with the sharing of injecting paraphernalia

Recent evidence suggests that the sharing of injecting paraphernalia may contribute to the spread of HCV (Crofts *et al.* 2000; Hagan *et al.* 2001; Mathei *et al.* 2006; De *et al.* 2008) and that IDUs report sharing injecting paraphernalia, such as cookers, filters and water more than they report sharing needles and syringes. Thus, we decided to modify our time since onset of injection model to allow for the transmission of HCV to occur through the sharing of (i) filters, (ii) filters and cookers and (iii) filters, cookers and water. Then, assuming that the self-reported needle and syringe sharing rates were correct, we used numerical simulations to see if the sharing of these items could account for the inability of our model to reproduce the epidemiological data for Glasgow. Using our numerical simulation package we estimated the transmission probability of acute and chronic HCV through these items by finding the transmission probabilities that gave us an endemic HCV prevalence that was within the 95% CI for HCV prevalence amongst all Glasgow IDUs (including naive and experienced IDUs).

We found that it was possible to reproduce the prevalence of HCV amongst all IDUs when we assumed that the only extra transmission source was filters, filters and cookers, or filters, cookers and spoons. However we were unable to reproduce the observed prevalence of HCV amongst naive and experienced IDUs. Our simulations indicated that the transmission probability of acute and chronic HCV through needles and syringes could be 4-5, 12 and 22 times greater than the corresponding HCV transmission probabilities through filter sharing, filter and cooker sharing and filter, cooker and water sharing respectively. The results of our simulations suggested that the transmission probability of acute and chronic HCV through the sharing of filters, cookers and water could be between 0.308%-0.351% for acute HCV and 0.114%-0.130% for chronic HCV. Therefore, it is important to determine if this risk is a viable method for HCV transmission.

This concludes the summary of the thesis. In the final section we shall discuss some future work ideas.

9.3 Future work

9.3.1 Updating the systematic review

Our systematic review discussed the evidence base on the risk of re-infection with HCV following spontaneous viral clearance amongst IDUs prior to 2009. Since research into the epidemiology of HCV amongst IDUs is ongoing, it is possible that our systematic review would need to be updated so that it incorporates any relevant research that has been published since the review was conducted. Although we have not formally repeated the review process, we did find a study which would have met our inclusion criteria if the review was repeated.

This study (published in Jan. 2010, subsequent to this review exercise) by Osburn *et al.* (2010) followed 22 active injectors for a median 702 days (IQR 505-1,397 days) after spontaneous resolution of their initial HCV infection. Those not previously infected were not followed up and so it is not possible to address the first two aims on the risk of acute re-infection and chronic infection among IDUs. Osburn *et al.* (2010) documented a total of 13 re-infections in 11 subjects (two subjects cleared two re-infections each). Even though the study was trying to determine if control of an initial infection conferred protection against future persistent infections, the results showed that five re-infections were of different genotype to that of the initial infection, whereas eight re-infections were same genotype infections. In a similar way to the Micallef *et al.* (2007) and Aitken *et al.* (2008) studies, the comparable proportions re-infected with either the same or a different genotype suggest that the risk of re-infection is not influenced by a past HCV genotype infection.

While this particular study would not change the conclusions in our systematic review, the ever changing evidence base means that it is possible that new research on the risk of HCV re-infection following spontaneous clearance could alter our conclusions. Therefore, it may be necessary to re-review the literature at some point in the future.

9.3.2 Pair approximations

Social contact patterns are important factors in the spread of infectious diseases, however, the contact patterns of IDUs is unclear. Models which allow for het-

erogeneity in injecting risk behaviour require data about the behaviour of IDUs in order to make accurate parameter estimates. For example, we need to know the average sharing frequencies for the different subgroups of high and low risk individuals, as well as the level of borrowing that goes on within and across subgroups. Previous models that have incorporated mixing between IDU subgroups have assumed either (i) random mixing, (ii) assortative mixing whereby IDUs will borrow most of their equipment from their own subgroup of the population or (iii) proportionate mixing where the number of contacts between members of two groups of IDUs is proportional to the activity levels and sizes of the groups.

The pair-wise approximation technique (Keeling and Eames 2005; Webb *et al.* 2007) is a novel approach which can be used to model the preferential interactions among IDUs, according to say how socially close they are within the population. These techniques offer a relatively low dimensional and sparing means of extending ordinary differential equation (ODE) models to incorporate a mixing structure (Keeling and Eames 2005) and can be used to capture the highly localised sharing relationships of IDUs as well as allowing for random interactions. Applying these techniques to IDU models in this way would require a modification to the standard use of pair-approximations which considers spatial separation rather than social separation. These techniques would extend the social structure of ODE models without substantially increasing the complexity of the model or the data needed to parameterise the model. Unlike network models, it is possible to obtain analytical solutions to pair approximation models. These solutions could then be used to highlight important factors for disease spread.

9.3.3 Drug resistant HCV infection

The ability of some infectious diseases to develop resistance to antiviral drugs is a major concern for the management of long term infections. For HIV, a number of studies have examined the possibility of drug resistant HIV strains and have modelled their transmission (Blower *et al.* 2001; Baggaley *et al.* 2005). Although treatment for chronic HCV is available, a number of those treated will fail to achieve SVR. In addition, IDUs may fail to complete their treatment programme because of the side effects associated with the current antiviral treatment method. Recent research has suggested that there may be some strains of HCV which

are now resistant to the new HCV antiviral drugs (Susser *et al.* 2009; Rong *et al.* 2010; Pawlotsky 2011). Therefore, it is important to determine how the emergence of antiviral resistant HCV infections affect the current and future prevalence of HCV amongst IDUs. As far as we are aware, there is no modelling work that has examined the transmission of antiviral resistant HCV infection amongst IDUs. Therefore, our future research would use previous modelling work on HIV resistance, such as the work by Blower *et al.* (2001), and the techniques used in this thesis to develop a mathematical model to examine the public health risk posed by antiviral resistant HCV infection.

Appendix A

Time since onset of injection model appendix

A.1 Constraint on s_{01} and s_{10}

Define m_0 to be the number of naive needles and syringes in circulation (as discussed in Subsection 6.2.1). Similarly define m_1 to be the number of experienced needles and syringes in circulation. Ignoring the infection status of the needles and syringes we obtain the following equations

$$\frac{dm_0}{dt} = \Lambda_{01}m_1 - \Lambda_{10}m_0 = \lambda_0 s_{01} n_0 - \lambda_1 s_{10} n_1, \tag{A.1}$$

$$\frac{dm_1}{dt} = \Lambda_{10}m_0 - \Lambda_{01}m_1 = \lambda_1 s_{10} n_1 - \lambda_0 s_{01} n_0, \tag{A.2}$$

where $\Lambda_{jk} = \dfrac{\lambda_j s_{jk} n_j}{m_k}$, $j, k = 0, 1$, denotes the rate at which an IDU in group j picks up a needle and syringe last used by a group k IDU and n_0 and n_1 are respectively the number of naive and experienced IDUs at time t. The above equations imply that at equilibrium

$$\Lambda_{01}m_1 = \Lambda_{10}m_0. \tag{A.3}$$

However equation (A.3) implies that $\lambda_0 s_{01} n_0 = \lambda_1 s_{10} n_1$. Note that $n_0 + n_1 = n$, the constant number of IDUs in the population and

$$\frac{dn_0}{dt} = \mu n - (\mu + \eta)n_0,$$
$$\frac{dn_1}{dt} = \eta n_0 - \mu n_1.$$

Hence as $t \to \infty$, $n_0 \to \mu n/(\mu + \eta)$ and $n_1 \to \eta n/(\mu + \eta)$ so this constraint becomes

$$\lambda_0 s_{01} \mu = \lambda_1 s_{10} \eta. \tag{A.4}$$

If this condition is not satisfied then equations (A.1) and (A.2) imply that one of m_0, m_1 eventually becomes negative. If condition (A.4) is satisfied then

$$\begin{aligned} \frac{dn_0}{dt} &= \mu(n_0 + n_1) - (\mu + \eta)n_0, \\ &= \mu n - (\mu + \eta)n_0. \end{aligned} \tag{A.5}$$

From (A.5) we have

$$\frac{d}{dt}\left[n_0 \text{exp}[(\mu + \eta)t]\right] = \mu n \text{exp}[(\mu + \eta)]t.$$

Integrating over $[0, t]$ gives

$$n_0(t)\text{exp}[(\mu + \eta)t] - n_0(0) = \frac{\mu n}{\mu + \eta}(\text{exp}[(\mu + \eta)t] - 1),$$

which implies that

$$n_0(t) = n_0^* + (n_0(0) - n_0^*)\text{exp}[-(\mu + \eta)t], \tag{A.6}$$

where $n_0^* = \mu n/(\mu + \eta)$. Using equation (A.5) and the fact that $n_1 = n - n_0$ we can use a similar argument to that used above to obtain

$$n_1(t) = n_1^* + (n_1(0) - n_1^*)\text{exp}[-(\mu + \eta)t], \tag{A.7}$$

where $n_1^* = \eta n/(\mu+\eta)$. Substituting (A.6) and (A.7) into equation (A.1) we find that

$$\begin{aligned}\frac{dm_0}{dt} &= \lambda_0 s_{01}(n_0^* + (n_0(0) - n_0^*)\exp[-(\mu+\eta)t]) \\ &\quad - \lambda_1 s_{10}(n_1^* + (n_1(0) - n_1^*)\exp[-(\mu+\eta)t]), \\ &= (\lambda_0 s_{01} n_0(0) - \lambda_1 s_{10} n_1(0))\exp[-(\mu+\eta)t].\end{aligned}$$

Integrating over $[0, t]$ we have

$$m_0(t) = m_0(0) - \frac{1}{\mu+\eta}(\lambda_0 s_{01} n_0(0) - \lambda_1 s_{10} n_1(0))(\exp[-(\mu+\eta)t] - 1).$$

Similarly

$$m_1(t) = m_1(0) - \frac{1}{\mu+\eta}(\lambda_1 s_{10} n_1(0) - \lambda_0 s_{01} n_0(0))(\exp[-(\mu+\eta)t] - 1).$$

Hence, as $t \to \infty$, $m_0(t)$ monotonically tends to

$$m_0(0) + \frac{1}{\mu+\eta}(\lambda_0 s_{01} n_0(0) - \lambda_1 s_{10} n_1(0)). \tag{A.8}$$

Similarly $m_1(t)$ monotonically tends to

$$m_1(0) + \frac{1}{\mu+\eta}(\lambda_1 s_{10} n_1(0) - \lambda_0 s_{01} n_0(0)). \tag{A.9}$$

So provided that both (A.8) and (A.9) are positive then $m_0(t)$ and $m_1(t)$ will approach strictly positive values. Furthermore, if the spread of HCV has been going on for a long period of time before the model is started we can expect that

$$n_0(0) \approx n_0^*(0) = \frac{\mu n}{\mu+\eta} \qquad \text{and} \qquad n_1(0) \approx n_1^*(0) = \frac{\eta n}{\mu+\eta}.$$

In this case we see from (A.8) and (A.9) that the number of needles and syringes in group will not change much from their initial values.

A.2 Derivation of ψ_0 and ψ_1

At time t, the total rate at which needles and syringes in the naive group are used is given by

$$(\Lambda_{00} + \Lambda_{10})m_0 = \lambda_0 s_{00} n_0 + \lambda_1 s_{10} n_1,$$

where n_0 and n_1 are respectively the number of naive and experienced IDUs. Also the total rate at which needles and syringes in the naive group are used or exchanged is given by

$$(\Lambda_{00} + \Lambda_{10} + \tau)m_0.$$

Hence the probability of choosing an unexchanged needle and syringe from the needles and syringes in the naive group given by

$$\psi_0 = \frac{\Lambda_{00} + \Lambda_{10}}{(\Lambda_{00} + \Lambda_{10} + \tau)}.$$

Similarly

$$\psi_1 = \frac{\Lambda_{11} + \Lambda_{01}}{(\Lambda_{11} + \Lambda_{01} + \tau)}.$$

A.3 Equivalence of IDU only and IDU and needle time since onset of injection models

Taking expressions (6.32)-(6.37) and substituting them into equation (6.1) gives

$$\begin{aligned}
\frac{d\pi_x^0}{dt} &= \mu - (\mu + \eta)\pi_x^0 - \lambda_0(1-\phi)s_{00}\pi_x^0 \frac{\Lambda_{00} + \Lambda_{10}}{(\Lambda_{00} + \Lambda_{10} + \tau)} \frac{1}{\pi^0}\big(\alpha_h(\pi_{h_1}^0 + \pi_{h_2}^0) + \alpha_y \pi_y^0\big) \\
&\quad - \lambda_0(1-\phi)s_{01}\pi_x^0 \frac{\Lambda_{11} + \Lambda_{01}}{(\Lambda_{11} + \Lambda_{01} + \tau)} \frac{1}{\pi^1}\big(\alpha_h(\pi_{h_1}^1 + \pi_{h_2}^1) + \alpha_y \pi_y^1\big), \\
&= \mu - (\mu + \eta)\pi_x^0 - \lambda_0(1-\phi)s_{00}\pi_x^0 \frac{\psi_0}{\pi^0}\big(\alpha_h(\pi_{h_1}^0 + \pi_{h_2}^0) + \alpha_y \pi_y^0\big) \\
&\quad - \lambda_0(1-\phi)s_{01}\pi_x^0 \frac{\psi_1}{\pi^1}\big(\alpha_h(\pi_{h_1}^1 + \pi_{h_2}^1) + \alpha_y \pi_y^1\big), \qquad \text{(using (6.19))}, \\
&= \mu - (\mu + \eta)\pi_x^0 - f_0 \pi_x^0,
\end{aligned}$$

which is equation (6.20) from our IDU only model. The equivalence of equations (6.2)-(6.12) can be checked in a similar way.

A.4 Derivation of $\boldsymbol{K}$=M($\boldsymbol{K}$)$\boldsymbol{K}$

Substituting in the equilibrium expressions for π_y^{0*}, π_y^{1*}, π_h^{0*} and π_h^{1*} given by (6.44), (6.48) and (6.50) into

$$K_0^* = \lambda_0 s_{00}(1-\phi)\psi_0^*(\alpha_h\pi_h^{0*} + \alpha_y\pi_y^{0*}) + \lambda_0 s_{01}(1-\phi)\frac{\psi_1^*\pi^{0*}}{\pi^{1*}}(\alpha_h\pi_h^{1*} + \alpha_y\pi_y^{1*})$$

we obtain

$$K_0^* = \left[\frac{\left(\lambda_0 s_{00}(1-\phi)\psi_0^*\left(\alpha_h + \frac{\sigma(1-\delta)}{\mu+\eta}\alpha_y\right) + \lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\right)\frac{1}{\mu+\sigma+\eta}}{1 + \frac{K_0^*}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)}\right.$$

$$\left. + \frac{\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\left(\alpha_h + \frac{\sigma(1-\delta)}{\mu}\alpha_y\right)\frac{\eta}{\mu+\sigma}\frac{1}{\mu+\sigma+\eta}}{\left[1 + \frac{K_0^*}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)\right]\left[1 + \frac{K_1^*}{\mu+\sigma}\frac{\mu+\eta}{\eta}\left(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)\right]}\right] K_0^*$$

$$+ \left[\frac{\lambda_0 s_{01}(1-\phi)\psi_1^*\frac{\pi^{0*}}{\pi^{1*}}\left(\alpha_h + \frac{\sigma(1-\delta)}{\mu}\alpha_y\right)\frac{1}{\mu+\sigma}\left(1 + \frac{K_0^*}{\mu+\sigma+\eta}\frac{\mu+\eta}{\eta}\right)}{\left[1 + \frac{K_0^*}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)\right]\left[1 + \frac{K_1^*}{\mu+\sigma}\frac{\mu+\eta}{\eta}\left(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\right)\right]}\right] K_1^*,$$

$$= M_{00}(\boldsymbol{K}^*)K_0^* + M_{01}(\boldsymbol{K}^*)K_1^*.$$

Here $M_{00}(\boldsymbol{K}^*)$ is the first term in the large square brackets multiplying K_0^*, $M_{01}(\boldsymbol{K}^*)$ is the second term in the large square brackets multiplying K_1^*, and $\boldsymbol{K}^*$=($\boldsymbol{K}_1^*$, $\boldsymbol{K}_2^*$).

Similarly

$$K_1^* = \Bigg[\frac{\big(\lambda_1 s_{10}(1-\phi)\psi_0^* \frac{\pi^{1*}}{\pi^{0*}}\big(\alpha_h + \frac{\sigma(1-\delta)}{\mu+\eta}\alpha_y\big) + \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\eta\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\big)\frac{1}{\mu+\sigma+\eta}}{1 + \frac{K_0^*}{\mu+\sigma+\eta}\big(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\big)}$$

$$+ \frac{\lambda_1 s_{11}(1-\phi)\psi_1^*\big(\alpha_h + \frac{\sigma(1-\delta)}{\mu}\alpha_y\big)\frac{\eta}{\mu+\sigma}\frac{1}{\mu+\sigma+\eta}}{\Big[1 + \frac{K_0^*}{\mu+\sigma+\eta}\big(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\big)\Big]\Big[1 + \frac{K_1^*}{\mu+\sigma}\frac{\mu+\eta}{\eta}\big(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\big)\Big]}\Bigg] K_0^*$$

$$+ \left[\frac{\lambda_1 s_{11}(1-\phi)\psi_1^*\big(\alpha_h + \frac{\sigma(1-\delta)}{\mu}\alpha_y\big)\frac{1}{\mu+\sigma}\big(1 + \frac{K_0^*}{\mu+\sigma+\eta}\frac{\mu+\eta}{\eta}\big)}{\Big[1 + \frac{K_0^*}{\mu+\sigma+\eta}\big(\frac{\mu+\eta}{\mu} + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\big)\Big]\Big[1 + \frac{K_1^*}{\mu+\sigma}\frac{\mu+\eta}{\eta}\big(1 + \frac{\sigma(1-\delta)}{\mu} + \frac{\sigma\alpha\delta}{\mu}\big)\Big]}\right] K_1^*,$$

$$= M_{10}(\boldsymbol{K}^*)K_0^* + M_{11}(\boldsymbol{K}^*)K_1^*.$$

Similarly to the above $M_{10}(\boldsymbol{K}^*)$ is the first term in the large square brackets multiplying K_0^* and $M_{11}(\boldsymbol{K}^*)$ is the second term in the large square brackets multiplying K_1^*.

Hence it is possible to write this system in the form

$$\boldsymbol{K}^* = \begin{bmatrix} K_0^* \\ K_1^* \end{bmatrix} = \begin{bmatrix} M_{00}(\boldsymbol{K}^*) & M_{01}(\boldsymbol{K}^*) \\ M_{10}(\boldsymbol{K}^*) & M_{11}(\boldsymbol{K}^*) \end{bmatrix} \begin{bmatrix} K_0^* \\ K_1^* \end{bmatrix} = \mathbf{M}(\boldsymbol{K}^*)\boldsymbol{K}^*.$$

If we examine the $M_{00}(\boldsymbol{K}^*)$, $M_{01}(\boldsymbol{K}^*)$, $M_{10}(\boldsymbol{K}^*)$ and $M_{11}(\boldsymbol{K}^*)$ terms more closely we can see that each term is greater than or equal to zero and strictly decreasing in K_0^* and K_1^*. In addition, we see that

$$\mathbf{M}(\boldsymbol{0})^T = \begin{bmatrix} M_{00}(\boldsymbol{0}) & M_{10}(\boldsymbol{0}) \\ M_{01}(\boldsymbol{0}) & M_{11}(\boldsymbol{0}) \end{bmatrix},$$

where

$$
\begin{aligned}
M_{00}(\boldsymbol{\theta}) &= \frac{\lambda_0 s_{00}(1-\phi)\psi_0^*}{(\mu+\sigma+\eta)}\left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{(\mu+\eta)}\right] \\
&+ \lambda_0 s_{01}(1-\phi)\psi_1^* \frac{\pi^{0*}}{\pi^{1*}} \frac{\eta}{(\mu+\sigma+\eta)}\left[\frac{\alpha_h}{(\mu+\sigma)} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\sigma)} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)}\right], \\
&= \kappa_{00},
\end{aligned}
$$

$$
\begin{aligned}
M_{01}(\boldsymbol{\theta}) &= \frac{\lambda_0 s_{01}(1-\phi)\psi_1^*}{(\mu+\sigma)} \frac{\pi^{0*}}{\pi^{1*}}\left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right], \\
&= \kappa_{10},
\end{aligned}
$$

$$
\begin{aligned}
M_{10}(\boldsymbol{\theta}) &= \frac{\lambda_1 s_{10}(1-\phi)\psi_0^*}{(\mu+\sigma+\eta)} \frac{\pi^{1*}}{\pi^{0*}}\left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{(\mu+\eta)}\right] \\
&+ \lambda_1 s_{11}(1-\phi)\psi_1^* \frac{\eta}{(\mu+\sigma+\eta)}\left[\frac{\alpha_h}{(\mu+\sigma)} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\eta)} + \frac{\sigma(1-\delta)\alpha_y}{\mu(\mu+\sigma)}\right], \\
&= \kappa_{01},
\end{aligned}
$$

and

$$
\begin{aligned}
M_{11}(\boldsymbol{\theta}) &= \frac{\lambda_1 s_{11}(1-\phi)\psi_1^*}{(\mu+\sigma)}\left[\alpha_h + \frac{\sigma(1-\delta)\alpha_y}{\mu}\right], \\
&= \kappa_{11}.
\end{aligned}
$$

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