MODELLING THE SPREAD OF HEPATITIS C VIRUS AMONGST PEOPLE WHO INJECT DRUGS

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Chapter 1

Introduction and Thesis Outline

There are countless developing health problems in the world. One of the most crucially overlooked is hepatitis C virus (HCV) which directly affects 3% of the global population (Akhtar et al. (2022)) and countless more indirectly. In a span of two decades after discovery, HCV has evolved to become the number one cause of liver disease globally (Shepard et al. (2005)). One of the prime examples of this phenomenon is Scotland. As a result of the abundance in resources, there is an ever-growing population of individuals that inject themselves with drugs. These individuals significantly increase the rate of infection and spread of the disease. In 2006 approximately 50,000 native Scottish citizens were positive for the HCV virus, with the largest group of these individuals being former people who inject drugs (PWIDs) (Hutchinson et al. (2006a)). Even with these growing numbers, the services aimed to reduce infection among PWIDs, with a focus on HCV and Human Immunodeficiency Virus (HIV), have been running since the 1980s. Though the services offered have very good results in the prevention of HIV, they have proven ineffective in the prevention of HCV. With this in mind, there are some recommendations within the Hepatitis C Action Plan courtesy of the Scottish Government (Goldberg et al. (2008)), that aim at improving intervention coverage among PWIDs alongside the prevention of further HCV infection. However, the dynamics of PWID populations alongside other factors associated with the prevalence of HCV in this group will be difficult to study.

Nevertheless, there are attempts made through the application of mathematical modelling techniques to recognize the link between the transmission of HCV and the risky behaviour witnessed among PWIDs. Additionally, these techniques are stretched further with the aim to comprehend the effect of strategies such as intervention plans, diagnostic techniques, treatment options and their combinations associated with the healthcare options linked to HCV (Corson (2011)).

Therefore, this thesis focuses on the analysis and development of mathematical models that assess and determine the HCV infection rate among PWIDs. These models are expected to be capable of being used to obtain real-time HCV prevalence estimates for Glasgow PWIDs. Moreover, we have changed the PWID needle interaction assumptions made by Corson et al. (2012) to allow needles to progress through different infectious stages and introduce treatment of infected PWIDs. These models are used to study how varying intervention measures and parameter estimates affect the spread of HCV in the population. Particularly, interest lies in determining control strategies and values of possible control parameters that can make eradication of HCV in Glasgow a reality. An example of this is using the model to ascertain the number of syringes and needles that can be distributed by the Glasgow and Clyde Health Board to mitigate the spread of HCV and continue until HCV is fully eradicated.

1.1 Thesis outline

In Chapter Two, we develop a model for HCV transmission among PWIDs through the sharing of needles and syringes. Utilizing analytical techniques, we conclude that the model behaviour is governed by the basic reproduction number R_0, with $R_0 = 1$ being a critical threshold dividing two different outcomes. It is noted that if $R_0 \leq 1$ only the disease-free equilibrium is present whereas if $R_0 > 1$ both the unique endemic equilibrium and disease-free equilibrium are present. The disease-free equilibrium of this model remains globally stable if $R_0 \leq 1$ but becomes unstable when the value increases above one. Following this step, the focus shifts to an approximate model. This approximation model has the same equilibria as those of the

full model. Also, we showed that if $R_0 > 1$ then the endemic equilibrium is locally asymptotically stable for our approximate model.

In Chapter Three, there are discussions on the parameter estimates applied in our simulations followed by presentations on the conclusions of the data discussed. Most of these parameter estimates are taken from Corson (2011) and Corson et al. (2012) which he derived from data and literature sources provided by Health Protection Scotland (HPS). The baseline estimates applied in the numerical simulations are subsequently introduced. With the use of these baseline parameter estimates one can determine the progress made in the elimination of HCV in the population. The ambiguity of the parameters is then examined and its effect on HCV prevalence as well as the trend taken by the model selected and making comparison with the results of Corson (2011).

In Chapter Four, we study the development of a mathematical model that splits the PWID population into two different groups. These groups are distinguished by their time since start of self-injecting behaviours and the introduction of different PWID needle interaction assumptions make the model analysis considerably more complex than previous work. We have also shown that the behaviour of the model is again controlled by the basic reproduction number R_0. We have seen that if $R_0 \leq 1$ and the disease is present in the population, in this case the system will tend toward the globally stable disease free equilibrium where HCV has been eliminated in all PWIDs and needles. We also prove that if $R_0 > 1$ then there is a unique non-zero equilibrium as well as the disease-free one. Lastly, we explore the behaviour of this model numerically.

In Chapter Five, the mathematical model extends further to incorporate the HCV transmission that is a result of needle sharing in individuals who inject themselves with drugs (Corson (2011) and Corson et al. (2012)). The main discussion focuses on the heterogeneity effects of this parameter where the drug injecting individuals are represented as a community of size n. This group is further split into p groups based on the frequency at which they share injection equipment where they share m needles in q shooting galleries. The key parameter of the models being derived is the Basic Reproduction Number symbolized by R_0. After that we

focus on the numerical simulations applied to determine how heterogeneity affects different groups within the PWID populations and the shooting galleries they have established. The aim is to carry out simulations based on realistic parameter values derived from sources in the literature.

In the last chapter which is Chapter Six, we summarise our thesis, give a general conclusion and also recommend some future works.

Note that we have used the literature review of the thesis of Corson (2011) as a template for our literature review because we have based our model on Corson's model so there is similarity in the background literature. Also, we have added many new references to reflect more recent work that has been done since Corson submitted his thesis. We have also added a new section on HCV treatment because there have been big advances in treatment since 2011. Also the next generation matrix was not discussed in Corson's thesis. Moreover, we have discussed the epidemic model, local and global asymptotic stability of rest points of systems of ODEs. We have mentioned the bifurcation, persistence, Quasi-steady-state-approximation and fixed point theorem. We also added a subsection on a technical way for computing R_0. We also discuss in detail the work of Corson and co-workers, heterogeneity models and the work of Greenhalgh and Al-Fwzan, different to Corson's thesis.

1.2 Hepatitis C virus

HCV is one of the diseases that affect millions of people globally and it is a blood-borne pathogen. It is a major worldwide health issue that requires extensive active interventions to control and stop it (WHO (2022)). Information about the worldwide distribution must be specified based on international research. HCV, a blood borne virus, is commonly transmitted by various practices used in people who inject drugs (PWIDs), such as sharing needles by PWIDs who ignored sterilising of needles.

HCV is a virus which is a single stranded RNA virus, which flows through the blood, leading to infection of the liver cells. It was discovered in 1989 and it is believed that it currently affects 58 million people throughout the world (WHO

(2022)). Acute and chronic infections can result from HCV. The former occurs in the first six months after the patient has been affected, in which spontaneous viral clearance can develop (Hoofnagle (2002) and Kamal (2008)). Symptoms which are displayed include fatigue and jaundice (Muzzi et al. (2005)). On the other hand, if HCV RNA is detected after this initial period, it is referred to as chronic HCV infection. Chronic HCV is more prominent as the majority of cases are asymptomatic and between 50% and 80% of those affected develop chronic HCV which puts them at the risk of liver disease in later years. Between 4% and 12% will develop cirrhosis within 20 years. Hepatocellular carcinoma, a form of cancer of the liver, will develop in up to 7% of those affected by cirrhosis and decompensated cirrhosis, liver failure, will occur in 6% of cases (Corson (2011)).

Distinct but related viral strains result as the HCV genome is mutable. One mutation per genome per replication cycle is generated. Six genotypes and a further six subtypes have been identified (Blackard et al. (2008)). No vaccine is available which can protect individuals against infection as the viral replication cycle creates about ten trillion new virus particles every day (Li et al. (2015)).

1.2.1 Treatment of HCV infection

Treatment by drugs is not recommended in the early stages of HCV which is known as acute hepatitis C virus infection (NHS (2020)). Martin et al. (2011) consider a model in which up to 6% of continuing PWIDs were treated annually. This is in line with observed treatment rates in the UK up to 2015 where at most 3% of PWIDs were treated annually (Martin et al. (2015)).

There are fewer treatments for those who have acute HCV. The main reason for this is that those with acute HCV tend to be asymptomatic, meaning the infection is difficult to diagnose. Moreover, there is the likelihood that acute HCV infection can clear spontaneously which means that treatment would not be required but could also be harmful in such instances (Corson (2011)).

Antiviral drugs are a means of treating those patients who are chronically ill. The most common drugs in use are Interferon (IFN) or a combination of Interferon and Ribavirin (Rihan et al. (2017)). These should be taken over a period of between

24 and 48 weeks. Both Pegylated and Non-Pegylated Interferon can be used, the half life of the former is longer than that of the latter, as well as having a slower rate of clearance (di Bisceglie and Hoofnagle (2002)). Pegylated Interferon-Ribavirin is the recommended treatment, however, it has to be taken into consideration that it is not 100% effective and there are a number of possible side effects. Treatment is considered as having success when patients have a sustained virological response (SVR) which means that there is no trace of HCV RNA in serum 24 weeks after the treatment has been completed (Corson (2011)).

However treatments for HCV have improved dramatically in recent years moving from relatively expensive and ineffective interferon based treatments to much more effective and cheaper Directly Acting Antiviral (DAA) treatments (Rihan et al. (2017)). DAAs are effective on a number of targets in the HCV virus. There are drugs that are only effective when they are combined with others, but not when they are used individually. The combination of DAAs drugs is always prescribed for between 12 and 24 weeks, and it is administered orally, specifically once or twice a day. Patients are not injected with the combination of DAAs drugs. There are cases where patients are only required to use one tablet because of the effectiveness of the drug (Mushtaq et al. (2020)).

So recently there has been a huge increase in the number of PWIDs being treated (Harris et al. (2019) and Traeger et al.). Traeger et al. (2020) state that in Australia DAAs have moved from a cumulative total of less than 1% of RNA tested PWIDs receiving treatment to a cumulative total of around 45% of RNA tested PWIDs (note that this is RNA tested PWIDs not all PWIDs). Moreover World Health Organization forward targets are even more ambitious with 80% of PWIDs to receive treatment by 2030 (WHO (2020)). According to the European guideline, DAAs should mainly be used to treat patients who have severe liver diseases, particularly with regard to the previous recommendations.

Needle and syringe programmes (NSPs) reduce the sharing of syringes and needles infected with HCV, while opioid substitution therapy (OST) reduces the frequency of injections thereby reducing the risk of sharing infected needles or syringes. When combined, these two techniques alongside actual treatment have shown signif-

icant reduction of HCV infection in the locations implemented (Martin et al. (2011) and Tod and Hirst (2014)). A larger study conducted by Turner et al. (2011), across six sites in the UK which analysed the impact of NSPs and OSTs identified that PWIDs who received OST were 64% less likely to be affected by HCV. Moreover, when there were high levels of both NSPs and OST the possibility of being affected by HCV fell by 80%, which identifies the benefits of combining both OST and NSP to reduce the transmission of HCV in the PWID population (Al-Fwzan (2015)).

1.2.2 Transmission

This section analyses the different ways in which HCV can be transmitted and identifies the risk of each.

Blood transfusion

In the United States, HCV is transmitted commonly through blood-borne infection and the studies show that during 2013-2016 there were 2.4 million people who were living with HCV (Schillie et al. (2020)). However, since the early 1990s blood products in developed countries have been screened to identify HCV antibodies. This has led to a significant reduction in the risk of HCV being transmitted (Donahue et al. (1992)). As a result, by 2004 the chance of being affected by HCV after a blood transfusion was thought to be 1 in 2,000,000 (Goldberg and Anderson (2004)). This is in stark contrast to those countries where screening does not take place, where the risk of HCV infection from transfusion is still high (Corson (2011)).

From mothers to children

In children with HCV virus it is not obviously the reason of liver diseases before adulthood (Leung et al. (2020)). Moreover much has been written about HCV being transmitted from mothers to children during pregnancy, however it is not common. It is believed that transmission can occur in utero but the chance of transmission is not clear (WHO, (2010)). It has been calculated that the risk of a child born to a mother infected by HCV, also being affected is between 3% and 7% (Goldberg and Anderson (2004)). On the other hand, there is a significant increase of children being

affected by HCV when the mother is co-infected with HIV. Indeed, it is considered that the risk increases to between 5% and 36% (Corson (2011)).

Sexual activity

Another risk of being affected with HCV has been identified as unprotected sex with a partner who has been infected or with multiple partners (Thitipatarakorn et al. (2022)). Therefore, HCV can also be spread via sex (WHO (2022)). It is, however, not considered to be one of the main sources of HCV transmission. In the USA it has been identified that sexual activity accounts for between 15% and 20% of acute HCV cases which have been reported (Corson (2011)). Various factors have been considered as adding to the risk, including whether the male affects the female or vice versa. Moreover, the risk is considered to be greater when one of the partners has detectable HCV RNA. In a study conducted in Egypt in 2005, it was found that the possibility of a female being infected by a male is 3% when there is detectable HCV RNA (95% CI 0-13%) whereas this was reduced to 0% when there was no detectable HCV RNA (95% CI 0-9%).

Needle contamination

To reduce HCV infections we need to focus on the sharing of infectious needles (Villano et al. (1997)). Being infected by needles is a risk that health care workers take. The risk of being infected by HCV is considered to be between 0% and 10% (Sulkowski et al. (2002)). On the other hand the risk from a single needle stick injury is estimated at 0.25% (Corson (2011)). There are several factors which can contribute to individuals being infected by needles, including how much and the nature of the tissue affected, the extent of RNA in the source, the kind of needle used, as well as the nature and application of policies adopted to limit the occurrence of occupational infections (Kamal, 2008).

Body piercing practices

Needles are also used in body piercing and tattoo practices, therefore there is a risk of HCV infection, although there is a lack of data on the extent of cases. The risk of

HCV infection is greater in unlicensed and unregulated locations, such as prisons, where unsterilized equipment is used. A meta-analysis of studies, conducted by Vescio et al. (2008) which examined the incidence and causes of HCV in prisons, to identify the risk factors and assess HCV seroprevalence in the prison environment, identified from 30 studies that tattooing contributes to the incidence of HCV. It was assessed that prisoners who are tattooed are at a risk of HCV which is three times greater than those who are not.

People who inject drugs

Transmission amongst PWIDs is a strong reason for increasing transmission of HCV (Scott et al. (2018)). In developed countries which have effective screening of blood products, the main cause of transmission of HCV is injecting drugs, using needles and syringes which have been shared (Bialek and Terrault (2006)). A report into HCV incidence in Scotland identified that drug use is the main risk factor in the transmission of HCV in Scotland, which is replicated in other developed countries (McDonald et al. (2012)). Indeed, it is even higher in England where it has accounted for 92.5% of cases. In Australia the figure is 80% and in USA 60% (Dore et al. (2003) and Alter (1999)).

PWIDs are at greater risk of being infected by HCV than HIV that because of environmental and viral factors (Hagan and des Jarlais (2000)). The probability of being infected by HCV is between 1.5% and 5% when an infected needle is used, whereas in the same conditions, the risk of being infected with HIV is between 0.34% and 2% (Vickerman et al. (2009) and Grebely and Dore (2011)). When it is considered that it is estimated that there are more than 13 million PWIDs throughout the world, it can be identified that there is a substantial future health and economic burden of HCV.

1.2.3 Worldwide prevalence of HCV among PWIDs

In this section, we show the prevalence of HCV among PWIDs globally to see how this disease is dangerous and try to explain some mathematical models relating to transmission of HCV through PWIDs. As well as in the next section and for

the same reason, we will give some information about transmission of HIV among PWIDs globally and then move on to explain some mathematical models relating to transmission of HIV among PWIDs.

HCV antibodies detected by enzyme-linked immunosorbent assays (ELISA) in saliva or serum indicates the prevalence of HCV in a literature review to analyse the global prevalence of HCV amongst PWIDs (Aceijas and Rhodes (2007)). Data from 57 countries were examined. A similar study by Nelson et al. (2011) also examined peer-reviewed databases and online resources to determine worldwide prevalence of HCV and hepatitis B virus (HBV) amongst PWIDs. This retrieved data from 77 countries. Furthermore, differences in study design may lead to variances in characteristics of sample populations and their characteristics. Therefore, estimates of the prevalence of HCV may not necessarily reflect the true figures (Corson (2011)).

Africa

HCV is increasingly becoming common among people who inject drugs (PWIDs) (Sambai et al. (2022)). Studies have shown that there are many different causes for transmission of HCV through PWIDs in Africa. One of the most important causes was when the patients were injected by the same needle for a long time and this needle was used by other patients. Additionally, poor sterilization techniques increase the likelihood of transmission. delete sentence

In 2008, the highest amount of HCV prevalence in the world was in Egypt (Elghitany (2019)). Additionally more recently, it has been estimated that the number of chronically infected PWIDs in Egypt is 32,997 (Mahmud et al. (2020)). Other African countries with a high risk of prevalence of HCV are Cameroon and Burundi. Kenya, South Africa, and Zambia are the African countries with the lowest level of HCV infections.

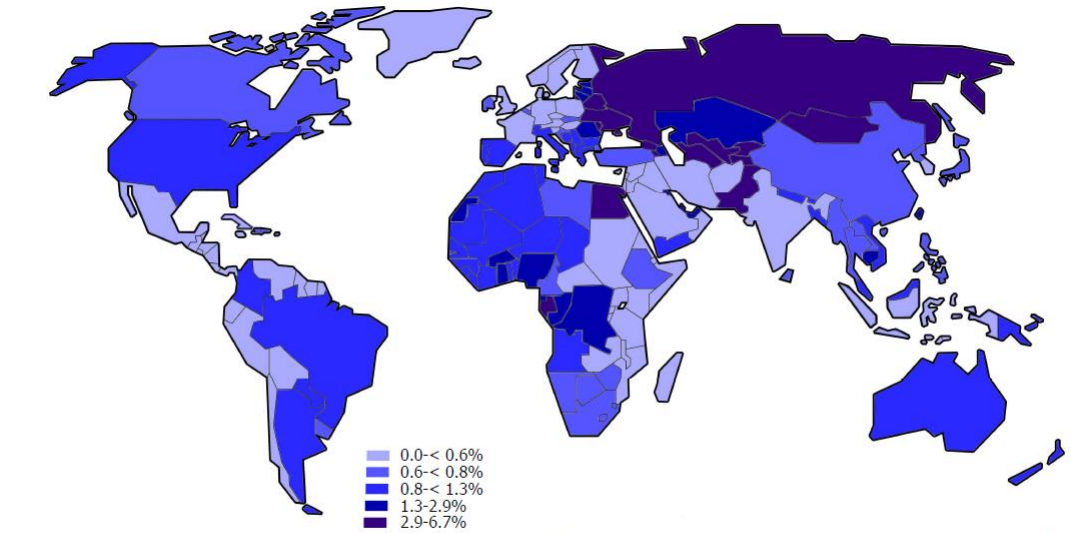

Figure 1.1: Global distribution and prevalence of HCV. (Adapted from Jefferies et al. (2018). Original sourece Gower et al. (2014).)

Moreover, HCV is still under-diagnosed and underreported in Africa except in Egypt. Moreover, in Africa the data on HCV has in the past been outdated (Karoney and Siika (2013)). The prevalence of HCV in Africa is estimated to range between 0.1 and 17.5, additionally that there is no clear or accurate information about HCV infection in the continent (Karoney and Siika (2013)). Hence, there is a need to further explore HCV in Africa.

Middle East

The Middle East and North Africa (MENA) is the region that is leading in HCV infections across the world as it accounts for about 20% of the total number of patients who suffer from the condition globally (Mahmud et al. (2020)). A significant number of people in the MENA are vulnerable to HCV because it is not only the epicentre of PWIDs but it also leads in drug production.

It is estimated that the numbers of PWIDs in Syria and Lebanon are less than 10,000. In these countries estimates of prevalence of HCV range from 5% to 60.5%. These estimates are based on studies of about 50 PWIDs (Salem et al. (2003)). The

prevalence of HCV among PWIDs has been estimated with highest rate in Israel, 67%, and the lowest is in Turkey, 28%, Nelson et al. (2011).

Eastern Europe and Central Asia

The highest number of prevalence of HCV is in Eastern Europe and Central Asia by more than 600,000 diagnoses (Pala and Remien (2021)). In both reviews it was found that the prevalence of HCV amongst PWIDs was above 50% in all countries except Hungary and Slovenia. The largest number of PWIDs was found in Russia where it was estimated that the number of PWIDs was between 1,500,000 and 6,000,000. Furthermore, the prevalence of HCVs in the PWID community in Russia was 96% (Nelson et al. (2011)) and HCV was most prevalent in the larger cities.

East Asia and South-East Asia

There were diverse estimates of HCV prevalence in this region, ranging from 33.5% to 99.3%. This diversity of estimates was most noticeable in China (Corson (2011)). HCV prevalence was estimated to be highest in Northern Thailand which had almost 50,000 PWIDs, with the highest numbers being found in Bangkok. In countries which had higher numbers of PWIDs it is estimated that HCV prevalence could be beyond 90%. In India, it is estimated that the PWID population is about 1,163,000, HCV prevalence was believed to be 92% (Aceijas and Rhodes (2007)). Furthermore, China has the highest number of people who inject drugs at 1,928,000. Japan, Hong Kong and Taiwan record a high rate of HCV prevalence of more than 50% (Nelson et al. (2011)).

Latin America and the Caribbean.

The estimates of HCV prevalence in Brazil varied between 39.5% and 69.7%. However, in the largest city, Sao Paolo, it was believed that as many as 84% of the PWID population had HCV (Segurado et al. (2004)). In this region, the lowest prevalence of HCV was considered to be in Columbia, where the estimate of HCV in one area of the country was 1.7%. Information from Mexico suggests that in those areas where data was available, HCV prevalence was as high as 100% (Corson (2011)).

North America and Western Europe

The USA, including a number of advanced countries, always has a low prevalence of chronic hepatitis C, even though this varies based on age and transmission factors (Jafri and Gordon (2018)). It is estimated that nearly 7 million people in the USA are suffering from HCV, which is equivalent to about 1.8% for the country's total population. Thus, the estimated prevalence rate in the USA is 1,800 per 100,000 persons. Based on recent estimates, the prevalence rate in the USA is 0.9%, which is similar to 2,936,000 people. In the USA, people who were born between 1945 and 1965 account for the majority of individuals with chronic HCV, a trend that is linked to a high rate of previous PWIDs in the age group.

Western European countries have a lower prevalence rate than the USA, even though they have witnessed some increase in the infection, which is associated with immigrants from nations where HCV is becoming endemic. However, Southern and Eastern Europe have a higher prevalence compared to the USA, mainly because of iatrogenic spread and PWIDs (Jafri and Gordon (2018)).

Australia and New Zealand

In New Zealand, the prevalence of HCV is unknown, but it is similar to that of Australia (Aluzaite et al. (2020)). Hence, estimates of HCV prevalence amongst the PWID population in Australia, taken from studies conducted between 1990 and 1995, varied from between 40% and 68% (Aceijas and Rhodes (2007) and Nelson et al. (2011)). Aitken et al. (2008) who conducted a study of 374 PWIDs in Melbourne between 2005 and 2007 found that HCV prevalence of those participants who contributed two blood samples was 71% (Corson (2011)).

1.2.4 Prevalence of HCV amongst PWIDs in Glasgow

Between 1990 and 1996 the prevalence of HCV amongst PWIDs in Glasgow fell from 79% in the former to 66% in the latter (Taylor et al. (2000)). However, this reduction was not observed in the subsequent years (NESI (2010) and Hutchinson et al. (2006b)). A study by the Needle Exchange Surveillance Initiative (NESI)

conducted between 2008 and 2009 of 2,513 PWIDs in Scotland found that HCV was most prevalent in Glasgow which accounts for an estimated 37% of PWIDs in Scotland (Hay et al. (2009)). The NESI study showed that the prevalence of HCV amongst Scottish PWIDs was 70%, 95% CI 67-73% (Corson (2011)).

1.3 HIV and AIDS

As we have concluded in our introduction regarding HCV, we will now provide some information about HIV and AIDS, especially its transmission and worldwide prevalence. The reason for introducing HIV and AIDS is because our mathematical model is based on previous studies that deal with the spread of HIV and AIDS through PWIDs. As a result, it is necessary to provide some information about HIV and AIDS in this section.

AIDS is currently one of the diseases that affect millions of people globally. AIDS is caused by the human immunodeficiency virus (HIV). There is a controversial debate about the origin and history of the HIV/AIDS pandemic. However, the history of HIV/AIDS can be traced back to the mid-1970s, even though the disease was unknown until the early 1980s when scientists started rigorous research to determine its cause and transmission.

AIDS was discovered in 1981 when gay men were diagnosed with Lymphadenopathy and unknown infection. Gay men in Los Angeles started showing a rare case of lung infections in 1981, even though they were previously healthy (Mor and Dan (2012)). Similar cases were reported among gay young men in New York and California who suffered from severe immune deficiency. Consequently, there was a global race to identify this strange disease. In 1983, Dr. Luc Montagnier of the Pasteur Institute in Paris identified a suspect virus, which was named LAV (Lymphadenopathy Associated Virus). He published his results in May 1983, giving the first definition of HIV.

At the same time, there was another scientific group led by Dr. Anthony Gallo of the National Cancer Institute in Washington that identified the causes of AIDS (Passi (2008)). Specifically, the National Institute of Cancer announced in April

1984 that they had discovered the cause of AIDS. A lot of studies have been done by various organizations since then to explore the disease. The biggest danger of the AIDS virus was that it affected the immune system and once infected with the virus a person will remain ill forever. Moreover, the associated symptoms vary over the life of the infection.

1.3.1 Transmission

HIV is transmitted differently in various countries. However, there are two main types of countries that show different ways in which HIV is transmitted from one person to another. Type I includes North America and Western Europe while type II incorporates Sub-Saharan Africa countries. In North America and Western Europe, HIV is spread mostly through homosexual men and PWIDs. In the USA for instance, it is estimated that nearly 50% of people with HIV are men who have sex with men (MSM) (Moore (2011)). Specifically, it is estimated MSM account for about 64% of people with HIV in North America (Moore (2011)). On the other hand, in North America, less than 28% of people with the disease have heterosexual orientation (Moore (2011)).

Therefore, HIV in North America is mainly transmitted through homosexual practices. Likewise, in Western Europe, MSM and PWIDs account for a significant majority of people with HIV/AIDS. Even though cases of HIV infections are reducing in many countries in Western Europe, countries like Germany, the United Kingdom (UK), and Belgium are experiencing a surge in infections due to the increasing number of MSM (Nakagawa et al. (2014)). Hence, homosexuality is the main cause of HIV infection in North America and Western Europe.

On the other hand, in Sub-Saharan Africa, HIV infections spread through heterosexual intercourse (Hay (1999)). Heterosexual sex is the main mode of transmitting HIV in Sub-Saharan countries in Africa. Consequently, unlike North America and Western Europe where HIV mainly affects men, in Sub-Saharan Africa, the majority of people who suffer from HIV/AIDS are women. Women in the region account for nearly 58% of HIV infections (Kharsany and Karim (2016)). Therefore, HIV is mainly transmitted through sexual contacts such as homosexual and

heterosexual activities.

Homosexual transmission

The cases of AIDs were discovered in North America in homosexuals (Robertson (2005)). After that, the community of homosexuals was reacting to this new disease in a different way. As a result, groups of scientists started to study this new unknown disease by using prediction models that are based on many parameters (McKusick et al. (1985a) and McKusick et al. (1985b)). In Scotland, there are high-risk sexual behaviours in homosexual men. HIV infections increased between 1996 and 2002 due to treatment optimism, especially based on the findings of various researchers (Hart and Williamson (2005)).

The nature of homosexual activities, including the behaviours and attitudes of gay people, is increasing the prevalence of HIV/AIDS in many developed countries, especially North America and Western Europe. MSM, for instance, have liberal attitudes towards sexual intercourse, which leads to both instantaneous and spontaneous behaviour that increases the risks of HIV infection (Mor and Dan (2012)). In addition, age-mixing is a common practice in gay sexual relationships, increasing the risk of exposure to HIV infections. Besides, homosexuality is increasingly being accepted in many developed countries like the USA, leading to increased tolerance and acceptance of the gay community. Gay people also have a high number of sexual partners, resulting in an increased prevalence of infection (Mor and Dan (2012)). Therefore, homosexuality is increasingly becoming one of the major factors that are contributing to HIV infections in North America and Western Europe.

Heterosexual transmission

Despite Europe and North America having a large number of cases of AIDS due to homosexual transmission, there are other parts of the world such as sub-Saharan Africa and the Caribbean whose transmissions are mainly through heterosexual intercourse. There are many different studies that conclude that HIV is transmitted less through heterosexual partners and these studies indicate the range of infection between 7% and 68% percent (Fischl et al. (1987)). In the Caribbean, for instance,

it is estimated that heterosexual transmissions account for between 60% and 80% of HIV infections while homosexual transmission only contributes close to 10% of total transmission in the country (Pape (2011)). The same trend is witnessed in many African countries. Thus, HIV transmission in some regions like Sub-Saharan Africa and the Caribbean mainly occurs through heterosexual transmission.

Needle Sharing

In many different parts of the world such as Edinburgh in the UK, New Jersey and Connecticut in the USA, Thailand and Italy, the large number of AIDS cases is because of drug injection (Des Jarlais et al. (1992)). There is no obvious reason for why addicts share needles, but it is possible that lack of access to sterilised needles is the main cause. The use of drugs is not acceptable from a community viewpoint for many reasons such as the links to crime. Moreover, the environment makes it possible for addicts to inject and share needles without cleaning and replacing them.

Consequently, many PWIDs are suffering from AIDS. The recent statistics reveal that between 0.9 million and 4.8 million PWIDs have been infected with HIV globally (Des Jarlais et al. (2016)). Needle sharing is believed to be the most efficient mode of transmitting HIV, resulting in the increasing cases of infections among PWIDs across the globe.

1.3.2 Worldwide prevalence of HIV/AIDS

Because we have based our model, in the next chapter, on the previous works which described the spread of HCV and HIV among PWIDs then as the previous section described the spread of HCV, we now move on to outline the spread of HIV/AIDS in some parts of the world. We start with the epidemics in Africa and end with Europe.

Africa

Heterosexual contacts and mother-to-child transmission account for the majority of cases of HIV infections in Africa. There were 2 million African deaths by AIDS in 1998. Also, there were more than 21.5 million adults and 1 million children with

HIV in the same year. As a result, because of the surge in infections and this risk, the United Nations (UN) set the targets of reducing the spread of HIV by 2015 (Kim and Watts (2005)). Based on the 2013 report, about 1.5 million Africans are suffering from HIV infection, indicating a significant reduction since 2005 (Kharsany and Karim (2016)). HIV infections in the continent have declined by about 33%, particularly between 2005 and 2013 (Kharsany and Karim (2016)). Nonetheless, the rate of HIV infection in the continent is still higher than in many regions in the world.

Asia

Because the majority of the world population is based in Asia, the level of risk of spread HIV/AIDS in the continent is higher than other parts of the world. For example, India has a population of over 1 billion, and half of them are in the age group of 15-49. Asia is increasingly becoming the epicentre of HIV infections due to its large and growing populations. According to the statistics that were released in 2007, nearly 4.9 million Asians were infected with HIV/AIDS (Rodrigo and Rajapakse (2009)).

Although there are many different countries in Asia which have a low rate of HIV infections, some Asian countries like Pakistan and Nepal have experienced a significant increase in infections. Some of the main factors that are facilitating the spread of HIV/AIDS in Asian include a surge in the number of PWIDS, poverty, and social taboos (Rodrigo and Rajapakse (2009)). Asia is likely to experience a surge in HIV infections due to its large population.

The Caribbean and Latin America

HIV/AIDS in the Caribbean and Latin America is mainly transmitted through homosexual contact and intravenous drug use. Over 2 million people are estimated to be living with HIV in the Caribbean and Latin America (Avert (2019)).

HIV/AIDS, therefore, is the leading cause of death in many parts of the Caribbean such as Jamaica and Guyana. In Latin America and the Caribbean, women are more vulnerable to HIV infections than their male counterparts (Sutherland (2014)).

Poverty is one of the main factors that are contributing to the high prevalence of HIV infections in the two regions as it leads to unhealthy behaviours such as prostitution. HIV/AIDS is still a major health challenge in the Caribbean and Latin America.

Western Europe and North America

In 2005 alone, nearly 65,000 people became infected with HIV, making the number of people living with HIV/AIDS in North America and Western Europe to increase to 2 million. The number of people in Western Europe and North America of cases in either homosexual males or drug users is higher than heterosexual contacts. MSM and PWIDs are abundant in many countries in Western Europe and North America, explaining why HIV infections continue to increase in the two regions.

We are now going to introduce the basic reproduction number and simple epidemic models then some of the mathematical machinery necessary to analyse these models, in particular local and global stability of rest points of ODEs, bifurcation, persistence and Quasi-steady-state-approximation. We need to introduce the basic reproduction number and the simple epidemic models to illustrate some of the concepts needed.

1.4 The basic reproduction number

The modelling of infectious diseases is dependent on critical factors, including the basic reproduction number, R_0, which helps to identify the potential of a disease to persist within a population. It can also help to determine whether the disease can be eliminated. The basic reproduction number is the average number of secondary cases generated by a single susceptible individual entering a completely susceptible population at equilibrium (Vynnycky and White (2010)).

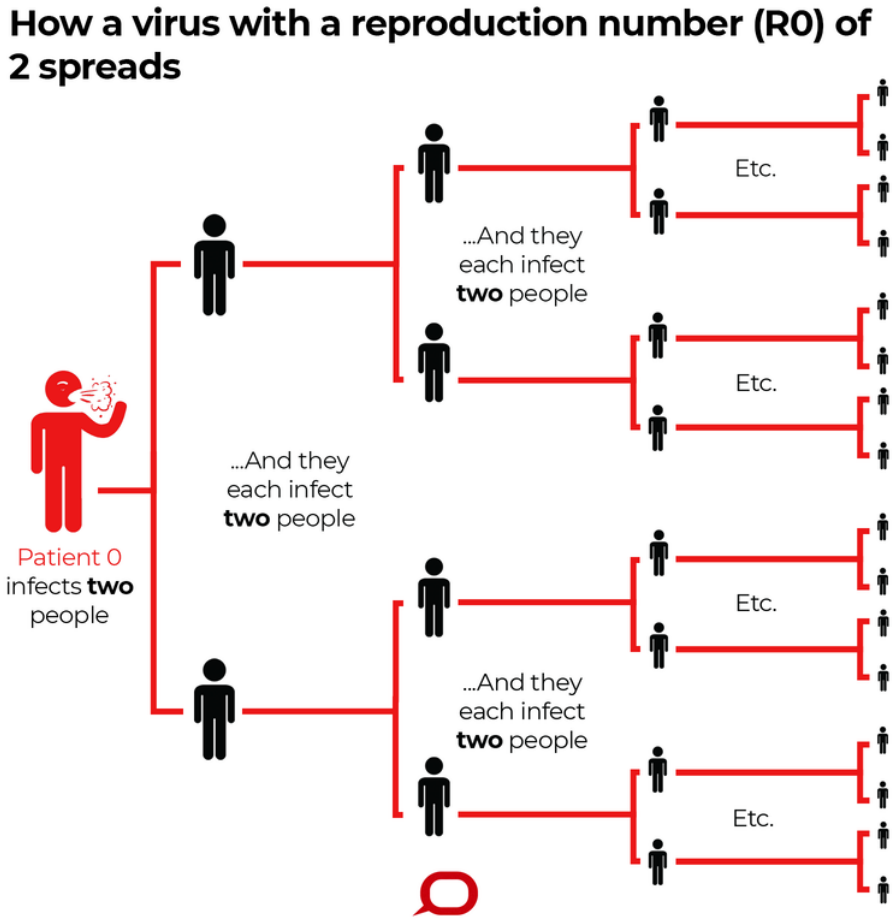

Figure 1.2: How a virus spreads when the basic reproductive number $R_0 = 2$. (Adapted from Eisenberg (2020a). Original figure in Eisenberg (2020b).)

In Figure 1.2, which outlines the effects of an infectious disease when $R_0 = 2$ through different time periods, it can be seen that the number of those infected doubles in each time period. This signifies that there is an epidemic which continues to grow until the process abates due to the decreasing number of individuals who are susceptible to the disease.

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

Table 1.1: Basic reproduction numbers for various well known infectious diseases (taken from (Corson (2011)).

From Table 1.1 above it can be seen that the reproduction number differs in different diseases. Factors which contribute to the spread of the disease include those which relate to the population in question at the time period, including healthcare available, preventive measures available and level of hygiene. Table 1.1 provides the basic reproduction number for various infectious diseases (Vynnycky and White (2010)).

The basic reproduction (or reproductive) number represented by the symbol R_0, is a measure for the spread of a disease within a completely susceptible population. It measures the expected number of new infections caused by one positive case in an unexposed population. Therefore, if $R_0 > 1$, the infected individual will spread the disease to the population and the number of infections will increase, but not if $R_0 < 1$.

1.5 The epidemic models

The number of individuals changes with time, then the total population size is a function $N(t)$, defined by

$$N(t) = S(t) + I(t) + R(t)$$

where $S(t)$ is the number of susceptible individuals, $I(t)$ is the number of infected individuals and $R(t)$ is the number of recovered individuals at time t. The **SIR** (Susceptible-Infective-Removed) epidemic model is given by the system of ODEs

$$\begin{cases} S'(t) &= -\beta IS, \\ I'(t) &= \beta IS - \alpha I, \\ R'(t) &= \alpha I, \end{cases}$$

with given initial conditions $S(0), I(0)$ and $R(0)$ (Kermack and McKendrick (1927)). The parameters α and β are respectively *the recovery rate* and *the transmission rate constant*. Adding all three equations in the previous system, we have $N'(t) = 0$, this mean that the total population size is constant, *ie* $N(t) = N(0)$ for all t.

If we assume that those individuals who recover become immediately susceptible to be infected again, then the SIR model can be written

$$\begin{cases} S'(t) &= -\beta IS + \alpha I, \\ I'(t) &= \beta IS - \alpha I. \end{cases}$$

This system of ODEs is called the **SIS epidemic model**, it is a simplification of the SIR epidemic model. Here $N = S + I$ and $N' = 0$. Since $S = N - I$, the SIS epidemic model can be rewritten as

$$I'(t) = \beta I(N - I) - \alpha I.$$

As detailed by Kermack and McKendrick (1927), the *basic reproduction number* of the disease can be defined by

$$R_0 = \frac{\beta N}{\alpha}.$$

1.6 Local and global asymptotic stability of rest points of systems of ODEs

Let f be a function sufficiently smooth on an open set $U \subset \mathbb{R}^n$, consider the ODE system

$$x'(t) = f(x(t))$$

Definition 1.6.1. *A point x^* is called an equilibrium point or singular point if*

$$f(x^*) = 0.$$

An equilibrium point x^* is called hyperbolic if none of eigenvalues of the Jacobian matrix $Df(x^*)$ have zero real part (Shub (2013)).

Near an hyperbolic equilibrium point, the system of ODEs $x' = f(x)$ can be linearized to the system $x' = Df(x^*)x$. In this case, we can give a classification of the hyperbolic equilibrium point:

- *x^* is a sink if all of the eigenvalues of the matrix $Df(x^*)$ have negative real part,*
- *x^* is a source if all of the eigenvalues of the matrix $Df(x^*)$ have positive real part,*
- *it is called a saddle if at least one eigenvalue has a positive real part and at least one eigenvalue has a negative real part.*

About the local stability, a sink is stable and a source is unstable, a saddle is always considered unstable (Perko (2013)).

Definition 1.6.2. *The system of ODEs is Lyapunov stable if for every $\epsilon > 0$, there exist $\delta > 0$ such that if $||x(0) - x^*|| < \delta$, then for every $\epsilon > 0$ we have*

$$||x(t) - x^*|| < \epsilon$$

and locally asymptotically stable if it is Lyapunov stable and there exist $\delta > 0$ such that if $||x(0) - x^*|| < \delta$ then

$$\lim_{t\to\infty} ||x(t)|| = 0$$

and globally asymptotically stable if for all $x(0)$

$$\lim_{t\to\infty} ||x(t) - x^*|| = 0$$

In other words, local stability of an equilibrium point defines as that if we put the system somewhere nearby the equilibrium point then it will move itself to the equilibrium point eventually but the global stability means that the system will

come to the equilibrium point from any possible starting point that means we do not need to start near the equilibrium point.

Returning to the SIS epidemic model, we have two equilibrium points, that are solutions of the equation $\beta I(N-I)-\alpha I=0$, the first equilibrium point $I_1^*=0$ is called a **disease-free equilibrium**, and the second equilibrium point $I_2^*=\dfrac{\beta N-\alpha}{\beta}$ is called an **endemic equilibrium**.

If the disease-free equilibrium is the unique equilibrium and it is locally stable it may not be globally stable because if you start from the disease-free equilibrium limit cycle behaviour or chaotic behaviour may occur.

The stability of the model

The stability of the SIS epidemic model depends of the value of R_0. If $R_0<1$, in this case, there is a unique equilibrium point, namely the disease-free equilibrium I_1^*. All solutions of the equation

$$I'(t)=\beta I(N-I)-\alpha I,$$

approach to $I_1^*=0$, so $I_1^*=0$ is globally asymptotically stable. If $I(0)=0$ then $I(t)=0$ for all time.

If $R_0>1$ then the disease free equilibrium point $I_1^*=0$ is unstable and all solutions starting with $I(0)>0$ approach I_2^*. In this case I_2^* is locally asymptotically stable and globally stable on the set if we consider the domain $\{I>0\}$.

1.7 Bifurcation

Let the dynamical system

$$x'=f(x,\mu),$$

with μ is real number called a parameter. When μ varies, the dynamical system produces a topologically equivalent dynamical system, but, there may exists a value μ_0 of μ such that the resulting dynamical system is not topologically equivalent to the first system. In this case, μ_0 is called bifurcation value. In general we speak of **bifurcation theory** (Kuznetsov et al. (1998)).

1.7.1 The forward and backward bifurcation

The previous models depend on the parameter R_0, there is the critical value of this reproduction number $R_0 = 1$, in fact, if $R_0 > 1$ there are two equilibrium points, and the endemic equilibrium exists, and if $R_0 < 1$ there is only the disease-free equilibrium.

Martcheva (2015a) states that "the bifurcation diagram is called a forward bifurcation diagram, since the endemic equilibrium bifurcates 'forward' and exists only for values of the reproduction number greater than one" and "there are cases in which the bifurcating endemic equilibrium exists for $R_0 < 1$. It is said that backward bifurcation occurs". From the cited definitions we see that the notions of forward and backward bifurcations are tied to the special notion of the reproduction number R_0 used in epidemiology and related areas. So if we take them as indicators of how epidemiologists use these terms, we can draw the following epidemiologist-generic diagrams:

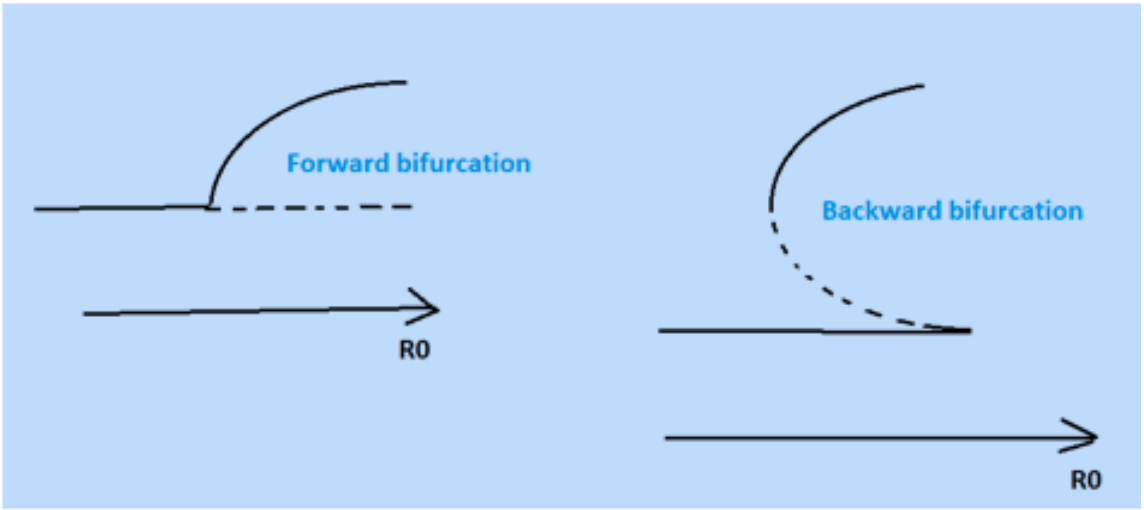

Figure 1.3: Forward bifurcation and backward bifurcation against R_0.

Depending on R_0, there is a bifurcation of the model. When the endemic equilibrium appears, for $R_0 < 1$, the bifurcation is called the **backward bifurcation**.

1.8 Persistence and Quasi-steady-state approximation

There are several definitions of the notion of the **persistence**, we use the simplest definition. Consider the dynamical system

$$x' = f(x),$$

with x in the closure of an Euclidean space E, such that ∂E is not empty (Butler and Waltman (1986)).

Definition 1.8.1. *The dynamical system $x' = f(x)$ with the initial condition $x(0) = x_0 \in E$, has a unique solution $x(t)$, the persistence means that*

$$\liminf_{t\to+\infty} d(x(t), \partial E) > 0, \ \ \forall x_0 \in E.$$

If the disease-free-equilibrium is unstable then we cannot have persistence and this happens when the solution of the dynamic system is periodic, as in the below example which is cited from Martcheva (2015a) we have

$$\begin{cases} S'(t) &= \Lambda - \beta(1+vI)IS - \mu S, \\ I'(t) &= \beta(1+vI)IS - (\alpha+\mu)I. \end{cases}$$

This example has an unstable equilibrium at

$$I = 0, \qquad S = \frac{\Lambda}{\mu}.$$

However it is not persistent (see Figure 1.4), because the system periodically returns to it, so

$$\liminf_{t\to\infty} f(t) = 0.$$

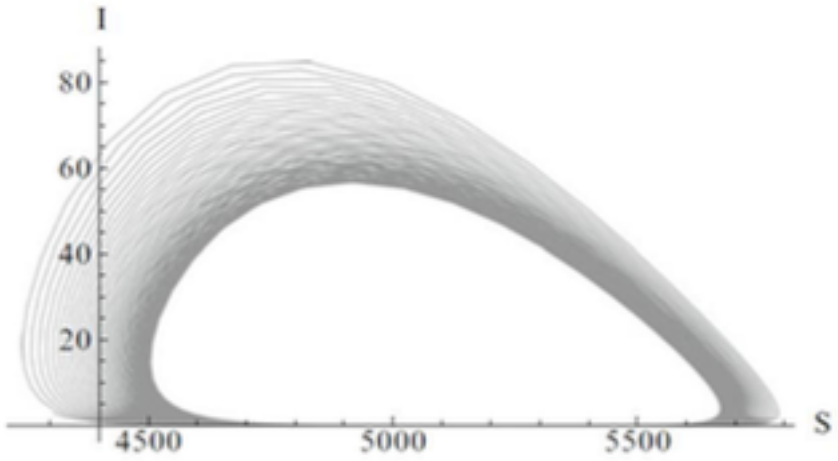

Figure 1.4: The diagram shows fluctuations in the (S, I)-plane the converge to a periodic orbit (taken from Martcheva (2015a)).

Definition 1.8.2. *The **quasi-steady-state approximation (QSSA)** is a method for reducing the number of variables in a dynamical system that includes processes on different time scales that can be separated into slow and fast. Indeed, a fast process is always considered in a steady state, by changing the time scale, on slow time scale, the state of the process changes (Cangelosi et al. (2018)).*

The QSSA replaces such variables which vary on much faster time scales than other variables and tend asymptotically to steady values dependent on the slow variables by their asymptotic steady values. More specifically, suppose the dynamic system in standard form has

$$x = \{x_1, ..., x_k\}, \qquad y = \{y_1, ..., y_m\},$$

$$x' = F(x, y), \tag{1.8.1}$$

$$y' = G(x, y), \tag{1.8.2}$$

$$scale(F_i) >> scale(G_j). \tag{1.8.3}$$

Inequality (1.8.3) is meant to be understood qualitatively as follows:
Given fixed values of y, equation (1.8.1) has solutions which reach steady state with

constant and finite values of x on time scales which are much shorter than the time scales on which solutions of (1.8.2) with fixed x vary (Cangelosi et al. (2018)).
Then a QSSA solution of system (1.8.1)-(1.8.2) is obtained as follows:
First we solve (1.8.1) with constant y for y in the range of all possible relevant values and make sure the solution asymptotically approaches some constant values:

$$x(t, y) \to x^*(y).$$

Then we solve (1.8.2) with x replaced by x^*:

$$y' = G[x^*(y), y].$$

1.9 Fixed point theorem

In this section we shall introduc some information relating to fixed point theorem which we need to use in Chapter 4. Therefore, let X be a Banach space, $K \subset X$ a convex and compact set.

Theorem 1.9.1. *Every continuous mapping $f : K \to K$ has a point x such that $f(x) = x$ (Elworthy and Tromba (1970)).*

Definition 1.9.1. *A subset $C \subset X$ is called a cone if for $a \in C$ then we have $ax \in C$ for any positive scalar x.*

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 at $\boldsymbol{K} = \boldsymbol{0}$ in the direction of the cone C. A bounded linear operator is an operator that maps every bounded set into a bounded set (Kreyszig (1978)).

Theorem 1.9.2. *(Theorem 6.2, Corson 2011, Theorem 4.4.3 Gatica and Smith, 1977) "Considering $T : C \to C$ as a compact continuous operator acting on a Banach space, such that $T(\boldsymbol{0}) = \boldsymbol{0}$ and T is Frechet differentiable at $\boldsymbol{K} = \boldsymbol{0}$ in the direction of the cone. After that we assume T satisfies*

1. *$T'(\boldsymbol{0})$, the Frechet 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*

2. *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 $|\boldsymbol{x}_0| = R$.

Note that we will use this theorem in Chapter 4 to prove our Theorem (4.4.2).

1.10 Technical way to calculate R_0

Scientists should first understand both the structures and interactions of the model to accurately estimate and apply the basic reproduction number. Consequently, there is a need to review or conduct further research on the basic reproduction number to either simplify the process or reduce the variation of its values that have been reported by different scientists across the globe. Besides, further research on the basic reproduction value can reduce misconceptions and confusions that have been witnessed, particularly during an infectious disease outbreak.

The reproduction number gives a threshold condition under which the disease-free equilibrium state is stable or unstable. By requiring stability of the disease-free state, the reproduction number can be expressed in terms of an equation. This can be done even for higher-dimensional models, but requires the computation of the the Jacobian, evaluated at the disease-free steady-state. Restricting that all eigenvalues have negative real part is equivalent to the stability of this equilibrium. In a 2x2 matrix, this is equivalent to $\mathrm{Tr}J < 0$ and $\det J > 0$. In the case of higher-dimensional systems, see the Routh-Hurwitz Criterion (Martcheva (2015b)).

Despite a representation for the stability of the equilibrium, this expression for the reproduction number may be written in more than one way. However it is assumed the expression should satisfy the following criteria:

- The reproduction number is nonnegative

- Zero transmission implies zero reproduction number
- The reproduction number is interpretable as the secondary infected count

In higher dimensional systems, the stability of the disease-free equilibrium is determined by the stability of the linearized system, i.e. the Jacobian evaluated at the equilibrium. Generally, this cannot be reduced to a 2x2 system, and thus stability is determined by finding the roots of the characteristic polynomial, of arbitrary degree. The reproduction number is the constant term in the polynomial, with the sign determined by whether the reproduction number is greater or less than one. To determine the stability, the Routh-Hurwitz Criteria give necessary and sufficient conditions for the roots of the characteristic polynomial to have negative real parts (Martcheva (2015b)).

1.10.1 Next generation matrix

Calculating the basic reproduction number for the complex models is not easy, particularly through a heterogeneous population. The basic reproduction number, which is also known as the basic reproduction ratio, is primarily utilized to describe the transmissibility of infectious diseases or agents. Besides being affected by a number of biological, environmental, and socio-behavioral factors, the basic reproduction number is estimated by different forms of complicated or complex mathematical models. Consequently, there is a high possibility of misrepresenting or misinterpreting of the basic reproduction number. Besides, it is not always measured directly as its values are determined by both model structures and assumptions. In addition, a significant number of the basic reproduction numbers that are reported in the scholarly literature are outdated or obsolete. Thus, scientists must use or apply the basic reproduction number with a lot of caution as its basic metrics are complicated or complex. Nonetheless, Diekmann et al. (1990) helped in improving the theory that can be used to generate the basic reproduction number for the models.

As detailed by Hurford et al. (2010), despite its potential to significantly simplify the usual linear stability analysis from the theory of dynamical systems, the next-generation matrix theory of Diekmann, Heesterbeek and Metz (1990) and van

den Driessche and Watmough (2002) has seen relatively little traction, in particular, in evolutionary invasion analysis. Principally, it is used to compute the basic reproduction number, $\mathcal{R}_0$, i.e., the expected number of infections directly resulting from a single infection in a population of only susceptible individuals; and is predicated primarily on the next-generation theorem (NGT) of van den Driessche and Watmough (2002):

Theorem 1.10.1. *Let*

$$x' = \boldsymbol{A}\boldsymbol{x},$$

with $\mathbf{x}_0 = \mathbf{x}(0) \neq \mathbf{0}$ *be a linear system of ordinary differential equations for* $\mathbf{x} : \mathbb{R} \to \mathbb{R}^n$ *and non-singular* $\boldsymbol{A} \in \mathbb{R}^{n\times n}$, $n \in \mathbb{N}$. *Let* $s : \mathbb{R}^{n\times n} \to \mathbb{R}$ *denote the spectral bound, i.e., the maximum real part of all eigenvalues of its argument and* $\rho : \mathbb{R}^{n\times n} \to \mathbb{R}$ *the spectral radius, i.e., the maximum absolute value of all eigenvalues of its argument. Then given any* $\boldsymbol{F}, \boldsymbol{V} \in \mathbb{R}^{n\times n}$ *such that* $\boldsymbol{F} \geq 0$ *and* $\boldsymbol{V}^{-1} \geq 0$ *(has all nonnegative entries),* $s(-\boldsymbol{V}) < 0$ *and* $\boldsymbol{A} = \boldsymbol{F} - \boldsymbol{V}$, *then*

$$s(\boldsymbol{A}) \lessgtr 0 \iff \rho(\boldsymbol{F}\boldsymbol{V}^{-1}) \lessgtr 1.$$

Thus by the NGT, the usual linear stability analysis to confirm that $s(\boldsymbol{A}) < 0$, may equivalently be replaced by checking instead $\rho(\boldsymbol{F}\,\boldsymbol{V}^{-1}) < 1$ for suitable $\boldsymbol{F}$, $\boldsymbol{V} \in \mathbb{R}^{n\times n}$. In particular, the special case when $\boldsymbol{x}$ lists the number of individuals of each of n classes in a structured population, $\boldsymbol{F}$ the *nonnegative* rate of generation of individuals in each class j from each class i, $1 \leq i, j \leq n$, and $\boldsymbol{V}$ the migration between and destruction of these classes; results in the *next-generation matrix* $\boldsymbol{F}\,\boldsymbol{V}^{-1}$ listing the expected (lifetime) number of individuals from class i generated by each class j, and $\rho(\boldsymbol{F}\,\boldsymbol{V}^{-1}) = \mathcal{R}_0$.

The latter expression (i.e. R_0) indicates the long-term expected lifetime or generation (of all classes combined) i.e. the long-term expected birth or reproduction number. And in particular $R_0 < 1$ indicates by the NGT that $s(\boldsymbol{A}) < 0$ i.e. the disease-free equilibrium $\boldsymbol{x}=\boldsymbol{0}$ is globally asymptotically stable meaning that $\boldsymbol{x}\to\boldsymbol{0}$ as $t \to \infty$ for all $\boldsymbol{x}_0$, whereas there will be no endemic equilibrium $\boldsymbol{x}$. In the case $\mathcal{R}_0 = 1$, there may or may not be a disease-free equilibrium and if there is it may or may not be either locally or globally stable. Additionally if $\mathcal{R}_0 = 1$, there may

or may not be an endemic equilibrium and if there is it may or may not be either locally or globally asymptotically stable. If $\mathcal{R}_0 > 1$ the endemic equilibrium will not be globally asymptotically stable on the whole space (because the disease-free equilibrium exists) so neither type of equilibrium will be globally stable the disease-free equilibrium will not be locally stable and the endemic equilibrium may or may not be locally stable.

1.10.2 Calculating R_0 in our model

The definition of R_0 as the expected number of secondary cases caused by a single newly infected case was around long before the next generation matrix methods were introduced (Macdonald (1952), Kaplan (1989), Massad et al. (2001)). In host-vector models for diseases such as malaria it was accepted that there were two definitions for R_0 in use, one corresponding to using humans as the only infectious unit and the second one corresponding to using both humans and mosquitoes as infectious units. The latter corresponds to the next generation matrix method and if it denoted by $\tilde{R}_0$ then the value of the basic reproduction number calculated using only humans as infectious entities is $\tilde{R}_0^2$. But both have the same threshold condition.

Diekmann and Heesterbeek (2000) define an h-state as the infectious state of an individual at the moment of birth and define k_{ij} as the expected number of new cases that have h-state i at the moment of birth. They define the next generation matrix to be (k_{ij}). So our use of the term "next generation matrix" in Chapter 4 corresponds to Diekmann and Heesterbeek's. They define $\boldsymbol{K} = (k_{ij}) \quad i, j = 1, 2, ..., n$ and

$$R_0 = \lim_{n\to\infty} ||\boldsymbol{K}^n||^{\frac{1}{n}}$$

and R_0 is the dominant eigenvalue of $\boldsymbol{K}$. If Diekmann and Heesterbeek's method is to make sense it must be independent of the choice of what constitutes an infectious entity at least in the resulting threshold condition.

The idea of the basic reproduction number and its meaning for systems with potentially more than one infectious state predates the work of Van den Driessche and Watmough (i.e. malaria Macdonald (1952)). Hence we would hope that these two different definitions of R_0 would be related and at least give the same threshold

(similar to the two definitions $\tilde{R}_0$ and $\tilde{R}_0^2$ for malaria). If we consider our method in Chapter 4 and the method of Van den Driessche and Watmough in context of the R_0 definition of Diekmann and Heesterbeek (1990) we can see that our method attempts to define an infected entity as a newly infected human, whilst the method of Van den Driessche and Watmough defines an infected entity as either a human or needle entering a new infectious state. The intergenerational time will thus be different for the two cases. But as the next generation matrix for Van den Driessche and Watmough's method is irreducible we expect that all infectious classes exponentially decrease at the same rate the two methods give different definitions of the expected number of entities infected at each generation and different ways of calculating them but it seems intuitive that if iterating our next generation matrix gives a discrete process that does not die out then the same should be true of the process of Van den Driessche and Watmough and vice-versa. Whilst this is not a rigorous proof it gives an idea of why we expect the two definitions to give the same threshold value (as indeed we have shown for the model discussed in Chapter 2) and this could form the basis of a rigorous proof.

1.11 Mathematical modelling of the spread of HIV amongst PWIDs

Mathematical modelling techniques have contributed to the understanding of the epidemiology of HIV, and the various risk factors to those susceptible to infection within PWID populations. Furthermore they have contributed to the evidence to support various interventions to tackle the spread of infection in PWID populations.

1.11.1 The model of Kaplan (1989)

One of the earliest mathematical models created to examine the spread of AIDS and HIV in PWID communities was developed by Kaplan (1989) who used models to gain an insight into the impact of PWIDs sharing needles on the transmission of

HIV. Kaplan's study identified those factors which were necessary to gain an understanding of how HIV was transmitted in such circumstances. Amongst the factors identified were the rates of needle and syringe sharing, the length of sharing and whether or not syringes and needles were cleaned. The latter also led to the model investigating the effectiveness of bleaching and the distribution of clean needles and syringes. Kaplan made the following assumptions to develop the model.

1. The number of needles or syringes in the shooting gallery is denoted by m.
2. The frequency of visits to shooting galleries is represented as a. Each PWID injects once on each occasion, therefore it is assumed that a represents the rate of needle and syringe sharing per capita.
3. It is assumed that once it has been used by one infectious PWID then all equipment is considered infectious. However, if equipment is used by an non-infectious PWID, it is the probability of flushing the needle, that is replacing the infected blood by uninfected blood (with probability θ), which means that the use of infectious needles puts non-infectious PWIDs at risk of HIV, that risk is removed for the PWIDs who subsequently use the equipment.
4. α denotes the probability of the transmission of HIV from shared equipment in each injection. It is assumed therefore that PWIDs can only be infected if injection is through shared needles and syringes.
5. As it is assumed that the PWID population n is both large and constant, whenever the population is reduced whether by a PWID dying, being imprisoned, hospitalised, or receiving treatment, then that individual is replaced by another susceptible PWID. The rate (per capita) at which PWIDs enter or leave the population under study is denoted by μ.

Kaplan devised two differential equations to determine the spread of HIV, the first equation describes how the fraction of infected PWIDs varies over time and the second equation describes how the fraction of infected needles change over time.

Therefore, the system of deferential equations was given by:

$$\begin{cases} \dfrac{d\pi(t)}{dt} = [1-\pi(t)]a\beta(t)\alpha - \pi(t)\mu, \\ \dfrac{d\beta(t)}{dt} = ab\pi(t) - ab\beta(t)[1-[1-\pi(t)](1-\theta)], \end{cases}$$

where $\pi(t)$ refers to the proportion of PWIDs within the population who are infected at time t and $\beta(t)$ relates to the proportion of infected needles and syringes at time t, with b representing ratio of PWIDs to needles.

A further equation was devised to represent the basic reproduction number. Hence, Kaplan derived R_0 as the expected number of secondary infections caused by a single infectious person entering a disease-free population of equilibria. This individual will visit shooting galleries at rate a per unit time and survive for average time $1/\mu$. Therefore this infected person will infect a/μ kits of injection equipment. The distribution of the number of PWIDs who use a needle before it is flushed is geometric with mean $1/\theta$. Each PWID is infected with probability α. Hence using this definition of R_0 then we have:

$$R_0 = \frac{a\alpha}{\mu\theta}.$$

For an epidemic to exist this must result in $R_0 > 1$. The results of the first numerical simulation show that when b is a large number, HIV reaches an equilibrium amongst this PWID population in a short time, whereas the disease spreads more slowly when b is a low value.

Kaplan also identified that heterogeneity played a role in needle and syringe rates of sharing and therefore introduced it into the model to determine the impact of heterogeneity on the results. It was identified, through numerical simulations, that those PWIDs who used and shared needles most frequently were infected quicker than those whose needle and syringe sharing could be considered moderate (Corson (2011)).

1.11.2 The model of Kaplan and O'Keefe (1993)

Following previous studies to identify risk factors of HIV and possible means of reducing the prevalence of the disease, Kaplan and O'Keefe (1993) continued looking at models to determine how HIV could be prevented from spreading in PWID

communities. Kaplan and O'Keefe (1993) developed a mathematical model which considered various factors listed below.

$$\begin{cases} \dfrac{d\pi(t)}{dt} = a[1-\pi(t)](1-\phi)\beta(t)\alpha - \pi(t)\mu, \\ \dfrac{d\beta(t)}{dt} = [1-\beta(t)]a\gamma\pi(t) - \beta(t)[\rho + a\gamma\theta[1-\pi(t))], \\ C(\tau) = \displaystyle\int_0^\tau [1-\pi(t)]a(1-\phi)\beta(t)\alpha dt. \end{cases}$$

The rate of needle and syringe sharing is represented by a. α provides the figure for probability of HIV transmission in each injection. The prevalence of HIV amongst those participating is denoted by $\pi(t)$. ϕ relates to the likelihood of the equipment being cleaned before being used. The rate of departure from the program is represented by μ. ρ relates to frequency of needle exchange. The ratio of those participating to the number of needles in circulation is denoted by γ. β denotes the proportion of needles where HIV is identified.

The model provided three equations, the first equation is for the fraction of infected PWIDs and uses the parameter α which is the probability of a non-infected PWID being infected from sharing equipment which has not been cleaned before use. The second equation represents equipment being affected after being used by a PWID who is infected. In this formula, it is identified that needles and syringes which are infected are assumed to be non-infectious if they are cleaned or exchanged prior to use. The final equation provides a calculation of the cumulative incidence of HIV during the time period. Furthermore the effectiveness of needle exchanges to prevent transmission of HIV amongst PWIDs had been questioned.

1.11.3 The model of Greenhalgh (1996)

Greenhalgh, a specialist on infectious diseases, (1996) modeled the effects of heterogeneity on the spread of HIV/AIDS among self-injecting drug users. This model let PWIDs vary their rate of visits to shooting galleries and take account of the cleanliness of the needles they use.

Greenhalgh (1996) modified the assumption that all PWIDs behave the same way and all needles and shooting galleries are the same (Kaplan (1989)). The dif-

ferential equations which described the spread of the disease are:

$$\frac{d\pi_i}{dt} = (1-\pi_i)\left(\sum_{j=1}^{q} \lambda_i p_{ij}(1-\xi_{ij})\alpha\beta_j\right) - \mu\pi_i, \qquad 1 \le i \le p \quad (1.11.4)$$

$$\frac{d\beta_j}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_i - \sum_{i=1}^{p} \Lambda_{ij}\beta_j\Big(1-(1-\pi_i)(1-\xi_{ij}(1-\theta))\Big), \quad 1 \le j \le q \quad (1.11.5)$$

with suitable conditions $1 \ge \pi_i(0) \ge 0$ and $1 \ge \beta_j(0) \ge 0$. The descriptions of the model parameters are presented in Table 1.2. Recall that R_0 is the key parameter which determines the behviour of the disease. Using the method below Greenhalgh found that R_0 is the largest eigenvalue of the $q \times q$ matrix $\boldsymbol{Q}_{jk}$, where:

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

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

This was based on directly calculating a matrix similar to the Next Generation Matrix used in the approach of Diekmnann et al. (1990) corresponding to the expected number of cases caused in each group by a single newly infected PWID entering a population of PWIDs and needles at the disease-free equilibrium. Because this approach considers infectious quantities to be only humans whilst the approach of Diekmann et al. (1990) considers both humans and needles as infectious entities two infectious generations in Diekmann et al.'s approach correspond to a single one in this approach, one would expect this R_0 to be the square of the one obtained by Diekmann et al.'s method.

The result in this model is if $R_0 \le 1$ the system of equations (1.11.4) and (1.11.5) has a unique equilibrium solution wherever the disease has been eliminated in each group of PWIDs and in each shooting gallery, and if $R_0 > 1$ and disease is initially present in either PWIDs or needles then the fractions of infected PWIDs and the fractions of infected needles tend to their unique equilibrium values.

In another study, Greenhalgh and Hay (1997) factored in an analysis of a version of Kaplan's model (1989), that showed that sometimes HIV or HCV infectious drug users did not always leave a needle infected alongside reduced sharing injecting equipment behaviour (Al-Fwzan (2015)).

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

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

1.11.4 The model of Greenhalgh and Lewis (2000)

Greenhalgh and Lewis conducted further studies in 2000 in which they developed the model of Kaplan and O'Keefe (1993) to relate it to AIDS and the three stages of infection which exist prior to its onset. Assuming that the infectivity of the last PWID to use a needle and syringe affected the infectivity of the needle and the syringe, using three stages allowed for PWIDs and the needles and syringes to be investigated at each of the different stages prior to the onset of AIDS. Doing so resulted in more positive predictions than previous models. The differential equations which described the spread of the disease are:

$$\frac{d\pi_A}{dt} = (1-\pi_A-\pi_B-\pi_C)\lambda(\beta_A\alpha_A+\beta_B\alpha_B+\beta_C\alpha_C)(1-\phi)-(\mu+\delta_A)\pi_A, \tag{1.11.6}$$

$$\frac{d\pi_B}{dt} = \delta_A\pi_A-(\mu+\delta_B)\pi_B, \tag{1.11.7}$$

$$\frac{d\pi_C}{dt} = \delta_B\pi_B-(\mu+\delta_C)\pi_C, \tag{1.11.8}$$

$$\frac{d\beta_A}{dt} = \lambda\gamma(\pi_A-\beta_A)-\beta_A\tau, \tag{1.11.9}$$

$$\frac{d\beta_B}{dt} = \lambda\gamma(\pi_B-\beta_B)-\beta_B\tau, \tag{1.11.10}$$

$$\frac{d\beta_C}{dt} = \lambda\gamma(\pi_C-\beta_C)-\beta_C\tau. \tag{1.11.11}$$

Equations (1.11.6)-(1.11.8) represent the behaviour of PWIDs at the stage A, at the stage B, at the stage C, whereas (1.11.9)-(1.11.11) represent the behaviour of infectious needles at the stage A, at the stage B and at the stage C. Moreover the stages A, B and C are different stages of HIV (Acutely Infectious, Asymptomatic and Pre-AIDS) which play a similar role to the different stages of HCV through which PWIDs pass in our model and also the optimistic model of Greenhalgh and Lewis (2001) was used as a template to build Corson's model because in both of them the PWID adopts the infectious stage of the last needle uses. Note that in this model there is again only one group of PWIDs and one group of needles.

Also λ, α_A, α_B, α_C, ϕ, μ, δ_A, δ_B, δ_C, γ and τ refer respectively to a needle and syringe sharing rate, probability of transmission on the stage A, probability of transmission on the stage B, probability of transmission on the stage C, probability that a PWID cleans a needle before use, per capita rate at which PWIDs leave the sharing, injecting population, per capita rate at which PWIDS move from stage A infection to stage B infection, per capita rate at which PWIDs move from stage B infection to stage C infection, per capita rate at which PWIDs move from stage C infection to full blown AIDS, the ratio of PWIDs to needles and needle turnover rate.

Recall that R_0 is the key parameter to determine the behaviour of the model therefore Greenhalgh and Lewis (2000) define R_0 by "the number of secondary infections caused by a single infectious person coming into a disease-free population at equilibrium". Greenhalgh and Lewis (2000) used a similar definition as in Kaplan (1989) and they defined R_0 as the total of secondary infections caused by one infectious PWID entering the disease-free population. Therefore, R_0 is given by:

$$R_0 = \frac{\lambda(1-\phi)}{(\mu+\delta_A)(\hat{\tau}+1)}\left[\alpha_A + \frac{\alpha_B\delta_A}{\mu+\delta_B} + \frac{\alpha_C\delta_A\delta_B}{(\mu+\delta_B)(\mu+\delta_C)}\right],$$

where $\hat{\tau} = \tau/\lambda\gamma$.

The main results of this model, show that if the basic reproduction number is less or equal to unity then the model has a unique equilibrium solution where HCV has died out in both PWIDs and needles. Otherwise, there is the disease-free equilibrium, but there is additionally a unique endemic equilibrium. The simulations

provided evidence that in both the model of Kaplan and O'Keefe (1993) and Greenhalgh and Lewis (2000) an endemic equilibrium would be reached after a period of about 50 years but that in the latter model there was a lower long term prevalence of HIV than in the former.

1.11.5 The model of Lewis and Greenhalgh (2001)

In 2001, Lewis and Greenhalgh also used the Kaplan and O'Keefe (1993) model to examine the three stages of infectivity (the same as A, B and C in the previous model) from the perspective that it is assumed that rather than it is that last infectious PWID user who has the main impact on the needle and syringe, it is the most infectious PWID who has the greatest impact on the equipment and therefore the predictions were pessimistic. The mathematical analysis followed along broadly similar steps to the study of Greenhalgh and Lewis (2000). Hence, Lewis and Greenhalgh (2001) adopted the assumption that the state of a needle after use is taken to be that of the more infectious of the state of the needle prior to use and the current PWID state therefore this assumption was a 'pessimistic assumption' compared with Greenhalgh and Lewis (2000) who use an 'optimistic assumption' (we will consider the same pessimistic assumptions when we deal with our model in the next chapters). So the system of differential equations (1.11.6)-(1.11.8) still represent the flow of PWIDs through the different infectious stages and the system of differential equations which describes the behaviour of infectious needles at each stage is:

$$\frac{d\beta_A}{dt} = \lambda\gamma(1-\beta_A)\pi_A - \beta_A(1-\pi_A)\phi\lambda\gamma - \beta_A\tau, \tag{1.11.12}$$

$$\frac{d\beta_B}{dt} = \lambda\gamma(1-\beta_A-\beta_B-\beta_C)\pi_B + \beta_A\pi_B\phi\lambda\gamma + \beta_C\pi_B\phi\lambda\gamma - \beta_B\pi_C\lambda\gamma - \beta_B\pi_A\lambda\gamma - \beta_B\lambda\gamma\phi(1-\pi_A-\pi_B-\pi_C) - \beta_B\tau, \tag{1.11.13}$$

$$\frac{d\beta_C}{dt} = \lambda\gamma\pi_C(1-\beta_A-\beta_C) + \lambda\gamma\phi\beta_A\pi_C - \lambda\gamma\beta_C\pi_A - \beta_C\lambda\gamma\phi(1-\pi_A-\pi_C) - \beta_C\tau. \tag{1.11.14}$$

Lewis and Greenhalgh (2001) used a similar definition and method as in Greenhalgh and Lewis (2000) and they give R_0 as:

$$R_0 = \frac{\lambda(1-\phi)}{(\mu+\delta_A)(\hat{\tau}+\phi)}\left[\alpha_A + \frac{\alpha_B\delta_A}{\mu+\delta_B} + \frac{\alpha_C\delta_A\delta_B}{(\mu+\delta_B)(\mu+\delta_C)}\right],$$

where $\hat{\tau} = \tau/\lambda\gamma$. Using analytical techniques, Lewis and Greenhalgh (2001) also found that the model behaviour is governed by the basic reproduction number R_0. Again, in comparison with the Kaplan and O'Keefe (1993) model the analysis showed that endemic equilibrium was reached sooner using the three stage model which also provided greater estimates of long term HIV prevalence.

1.12 Mathematical modelling of the spread of HCV amongst PWIDs

As for HIV mathematical modelling techniques have also been used to understand the intervention strategies to control the prevalence of the spread of HCV among PWIDs.

1.12.1 The model of Hutchinson et al. (2006a)

Hutchinson et al. (2006a), adopted a stochastic model which simulated the spread of HCV in PWIDs in Glasgow who shared needles and syringes. The models were used to provide an estimate of the prevalence and incidence of HCV in the city for the period between 1960 and 2000, of these estimates those from between 1988 and 2000 examined the number of infections that had been prevented through the use of intervention measures. The model also allowed an examination of the impact there would be if the infectivity of HCV was ten times as high in a period of six weeks after PWIDs had first been infected.

In the model three distinct infectious stages were employed and examined: susceptible, acute HCV and chronic HCV. Of these the acute stage was categorised into a short non-infectious phase and a longer infectious one, covering a period of up to two years. Those identified as being susceptible passed to the non-infectious acute

stage once they had been infected, after which they progressed to the infectious stage. From this point there were two possibilities, either the infection could be resolved and the PWIDs would return to the susceptible stage or the infection would become chronic. It was assumed that those who had successfully resolved the infection were partially immune to reinfection. It was considered that the likelihood of a new HCV viraemia being developed was halved and the likelihood of chronic infection developing was reduced twelve-fold. In order to estimate how often PWIDs injected and shared needles and syringes, surveys conducted in Glasgow in the 1990s were consulted.

1.12.2 The model of Vickerman et al. (2007)

Vickerman et al. (2007) analysed the transmission of HCV amongst PWIDs in London. Similar to the study of Hutchinson et al. (2006a) the model was used to examine the impact of intervention measures to reduce the sharing of needles and syringes amongst PWIDs who had been sharing needles and syringes for more than a year. The model focussed on those in the class of acute stage of HCV and sub-divided them into two categories, those who could resolve the infection spontaneously and those whose infection progressed to the chronic stage. It was assumed that those in the former group were immune to re-infection, whereas those in the latter group remain infected for life. Different transmission probabilities were assigned to each category.

The PWIDs were then further classified into three behavioural subgroups which related to the frequency of sharing needles: those who do not share, those whose sharing is infrequent and those whose sharing is frequent. The study determined that when sharing rates were reduced by more than 50%, HCV seroprevalence would fall in those PWIDs who had been injecting for more than eight years. Reductions of less than 25% would lead to a reduction in HCV for those PWIDs who had been injecting for up to four years. For HCV prevalence to be reduced to less than 10% there would need to be a reduction in baseline estimates of needle and syringe sharing from 16 events per month to only one or two. The simulations also indicate that significant decrease in HCV seroprevalence could only occur if interventions

were directed at the full PWID community. Furthermore, intervention would have to occur within the first year that PWIDs were injecting. Note that this model was also discussed deeply in Corson (2011).

1.12.3 The model by Corson et al. (2012)

A compartmental mathematical model was developed by Corson et al. (2012) to estimate HCV transmissions among PWIDs. This model was derived from a previous one by Vickerman et al. (2007). The aim of this model was to determine the level of needle sharing, cleaning and exchange necessary to promote HCV elimination among PWIDs in Glasgow. The model also enabled PWIDs progress through the many stages of HCV infection.

The population of PWIDs was split into individuals susceptible to HCV infection, x to represent those not previously infected, x_1 to represent those already infected, those in the acute clase of HCV infection (h_1 and h_2), those in the chronic stage of HCV infection y and those immune to HCV infection z (see Figure 1.5).

Corson et al. (2012) divided the infectious PWIDs into 'Acutely Infected' and 'Chronically Infected' classes corresponding to the observation that the level of virus in the blood is much higher in 'Acutely Infected' and 'Chronically Infected' PWIDs. Moreover the Acutely Infected PWIDs are divided into two classes corresponding to those who will progress to the chronic class (h_1) and those who will progress to the susceptible or immune class (h_2). The needles are divided into the same infectious classes as the PWIDs and again needles are assumed to adopt the infectious state of the last PWID to use them.

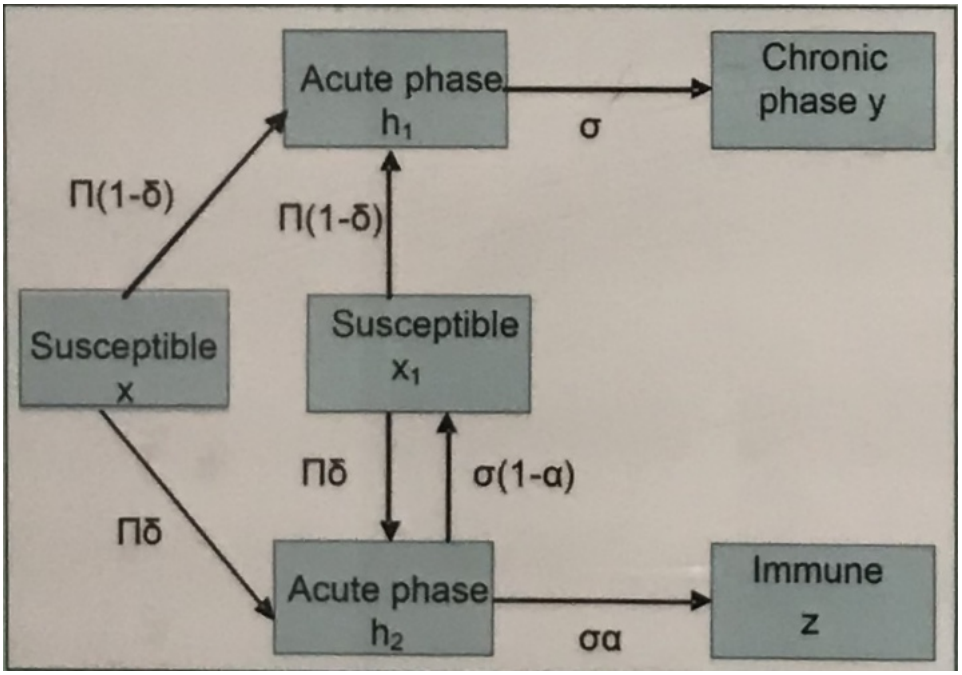

Figure 1.5: HCV transmission map. The arrows indicate the possible transitions for PWIDs between classes of HCV infection and the parameters are the per capita rate of flow between the classes (taken from Corson et al. (2012)).

Moreover Corson et al. (2012) assumed the size of the PWIDs population to be n, which is both large and constant. PWIDs who left the population due to a number of reasons like death or permanently avoiding injecting behaviour at a per capita rate of μ are instantly substituted by other susceptible persons. This simplifying assumption had been made in many other models of the spread of HIV and HCV amongst PWIDs. They developed this model to assess relevant intervention measures that were required to stop HCV among PWIDs who lived in Glasgow. Although the PWIDs population in Glasgow had remained unchanged for many years. So there was a possibility of expanding their model to give room for variable population size, mainly by utilizing methods previously employed by Caulkins and Kaplan (1991), Lewis and Greenhalgh (2001a) and Lewis and Greenhalgh (2001b). Therefore, the PWIDs population was grouped into three categories. The first category involved PWIDs who were susceptible to HCV infection, particularly through sharing needles and syringes. The category was further subdivided into x to denote PWIDs who had not initially been infected and x_1 to stand for those who had been

infected. The second category comprised PWIDs who were in an acute phase of HCV infection (h_1 and h_2). The final category involved PWIDs who had proceeded to the chronic phase of HCV infection (y), including those who could not be infected again due to immunity (z). Corson's model enabled two forms of acute HCV infection, which included the one that results in chronic infection and the other which caused self-limiting HCV infection. In the latter case the recovered individual re-entered the susceptible class.

Corson et al. (2012) denoted the mean per capita rate that PWID persons shared syringes and needles by λ while ϕ stands for the probability that a PWID will succeed in cleaning either their needle or syringe before he or she used it. To successfully clean needles or syringes, Corson et al (2012) assumed that individual PWIDs should used alcohol or bleach to eliminate the presence of HCV viral load before use. On the other hand, they denoted by α_h the probability that if a susceptible person injected himself or herself with a syringe in the phase of acute infection (denoted h_1 or h_2) without sterilizing or cleaning the needle then that person caught the disease. α_y stands for the corresponding probability of infection, when the syringe was in the stage of acute infectivity. Based on the data, α_h was more than α_y (Vickerman et al. (2007)).

Moreover, they considered the incorporation of probabilities of differential HCV transmission, which related to both acute and chronic infection, especially based on Hutchinson et al. (2006a), was the same as assumptions that were anchored on different blood viral loads, which were linked to the phases of HCV infection similar to HIV (Seitz and Muller (1994)). Furthermore the mathematical models of Greenhalgh and Lewis (2000) for HIV considered a high chance of spreading HIV for acute infection and chronic HCV infection. Thus in a similar way Corson et al (2012) decided to incorporate similar differential risks of HCV transmission in their model. Note that both HCV and HIV are blood born viral diseases spread amongst PWIDs.

Again Corson et al (2012) assumed that susceptible PWIDs who had contracted HCV will proceed to the chronic phase of infection, which was denoted by either h_1 or h_2. A percentage of δ of PWIDs who had just been infected with HCV were

allowed to proceed to the acute h_2 class. Based on Farci et al. (1992) and Micallef et al. (2007), Corson et al. (2012) assumed that the newly infected PWIDs were expected to spontaneously eradicate the virus when they finished their stay in this class with a proportion α expected to show immunity to HCV re-infection while the other proportion $1-\alpha$ became susceptible again and were capable of being re-infected with HCV. $1-\delta$, which was the remaining percentage of persons who had just been infected with HCV, were allowed to proceed to the acute h_1 class. On leaving the acute h_1 class the remaining PWID proceeded to the chronic infection stage where they stayed until they died or departed from the population that shares injections.

As well as modelling the PWID population, Corson et al. (2012) also modelled the number of needles and syringes by HCV infection status over time (needles can be uninfected, acutely infected or chronically infected). m denoted the total population size of needles and syringes. Only needles and syringes that had been used by PWIDs who were chronically or acutely infected can spread HCV. The infectivity of each needle was determined by the last infected PWID that it had come into contact with. Unused needles were uninfectious.

The force of infection experienced by a single susceptible PWID was given by $f = \lambda(1-\phi)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y)$. The authors therefore derived a system of nine differential equations, six of them describe the transmission of HCV among PWIDs and three describe HCV prevalence in needles.

Hence the system of governing equations that described the spread of HCV among PWIDs was given by

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

Parameter	Description
ϕ	Probability of needle cleaning
λ	Needle-and syringe- sharing rate
τ	Needle turnover rate
γ	PWIDs to needle ratio
μ	Rate PWIDs leave the sharing population
α_h	Acute HCV transmission probability
α_y	Chronic HCV transmission probability
$1/\sigma$	Period of the acute HCV stage
δ	Proportion that clears HCV infection
α	Proportion of PWIDs that become immune

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

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

This step was followed by an evaluation of the basic reproduction number R_0 which determines the behaviour of HCV among PWIDs. The total number of secondary infections caused by an individual infectious PWID entering the DFE is given by:

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

where the parameters are defined in Table 1.3, $\gamma = n/m$ is the number of PWIDs for each needle in the population and $\hat{\tau} = \tau/\lambda\gamma$.

This is not deduced directly by the next generation matrix. It is derived by considering directly a population of needles and PWIDs at equilibrium and a

single newly infected PWID entering it. Then Corson et al. (2012) consider a direct calculation of the average number of infectious needles caused directly by that PWID multiplied by the average number of PWIDs each needle infects. This method is commonly used for host vector models such as dengue and malaria (Greenhalgh et al. (2018), Macdonald (1952), Maier et al. (2017)). For dengue and malaria because the next generation method considers both PWIDs and syringes as infectious entities the R_0 calculated by this method for those diseases is the square of that calculated by the next generation method. Hence the threshold value for both models is the same. For our modified model we shall show how the R_0 value obtained using the definition of R_0 in Corson et al. (2012) is related to the R_0 value obtained by the next generation matrix method. Although the two values are different they are related and the threshold value is the same. A similar argument can be applied to the model of Corson et al. (2012). This result is original and was not obtained by Corson et al. (2012) even for their original model.

The main proposition of Corson's model, states that if $R_0 \leq 1$ the model has a unique equilibrium solution where HCV has died out in both PWIDs and needles. If $R_0 > 1$, there is the disease-free equilibrium, but there is a unique endemic equilibrium. Then, Corson et al. (2012) simulated HCV for the population of Glasgow PWIDs over time. The model parameters are estimated and they examine the behaviour of HCV when $R_0 \leq 1$ and $R_0 > 1$. Simulation has shown that when realistic parameter values are used the model tends to the endemic equilibrium value together with realistic parameter values resulting HCV prevalence estimated at 69% which matches up with observed data. Moreover, the authors examined the impact of various control measures on R_0. They determined the threshold values of sharing needle, cleaning and turnover that lead to R_0 less than unity and HCV elimination in PWIDs and needles. Note that this model was also discussed in Al-Fwzan (2015).

1.12.4 The model of Al-Fwzan and Greenhalgh (2015)

Al-Fwzan and Greenhalgh (2015) developed a mathematical model pertaining to the HCV infection rate among PWIDs sharing needles in shooting galleries. This model was based on an earlier simple model discussed by Corson et al. (2012), which

assumed homogeneity in time since onset of injection and needle sharing rates, and a model of Greenhalgh (1996) who showed the effects of heterogeneity on the transmission of AIDS and HIV among a population of injecting drug users. They compared that with the model by Corson et al. (2012). The model of Al-Fwzan and Greenhalgh (2015) focusses on the impact of heterogeneity in disease sharing rates and choice of shooting galeery on the prevalence of HCV in this risky group.

Al-Fwzan (2015) assumed that a population of n drug-injecting PWIDs is divided into p group sizes $n_1, n_2, ..., n_p$ where $n = \sum_{t=1}^{p} n_i$, where n is large and constant for each time t. The groups are uniform and distinct from one another in injection sharing rate, shooting gallery selection probability and needle cleaning probability. So there could be groups consisting of individuals sharing needles frequently or sporadically or never sharing needles. One premise underpinning the proposed model is that PWIDs do not change groups for the duration of their life or the duration of drug use. Moreover the groups are of constant size so that when PWIDs leave the population due to permanent cessation of injecting behaviour or death at per capita rate μ, they will immediately be replaced by other PWIDs susceptible to HCV infection who inject at the same rate and whose other characteristics are also similar. Furthermore, q shooting galleries are considered, with shooting gallery j comprising m_j needles or syringes, where $m = \sum_{j=1}^{q} m_j$ and m is large and constant for all time t. The shooting gallery visiting rate of every type i PWID is λ_i, with the probability of selection of shooting gallery j on every visit being P_{ij} for $j = 1, 2...q$, where $P_{ij} \geq 0$ and $\sum_{j=1}^{q} P_{ij} = 1$.

Upon visiting a shooting gallery, PWIDs undertake a single drug injection with a needle selected arbitrarily from the visited shooting gallery. PWIDs of type i are instantly replaced by other PWIDs at risk of HCV infection when they exit their group owing to terminating drug use or dying at per capita rate μ, they are replaced immediately by a susceptible PWID. The arrival rate of type i PWIDs at a presented needle in shooting gallery j is $\Lambda_{ij} = (\frac{\lambda_i n_i P_{ij}}{m_j})$. Al-Fwzan (2015) divided the population into p groups labeled $i = 1, 2, ...p$.

Al-Fwzan and Greenhalgh (2015) assumed that λ_i is the average rate that a type i PWID shares needles and syringes and ϕ_{ij} is the probability that a type i

PWID in shooting gallery j cleans his or her needle prior to use. α_h and α_y are respectively the transmission probability relating to acute and chronic HCV by shared needles and the average duration that a type i PWID remains in the acute stage is $1/\sigma$ time units. Also Al-Fwzan and Greenhalgh (2015) considered a needle turnover rate of the average rate at which PWIDs change their needles for clean needles in shooting gallery j of τ_j per year, PWIDs can be infected through the sharing of needles utilized by an HCV acutely or chronically infected PWID and that infectious needles do not lose their infectivity if they are left unused for a period of time. An infectious needle, when exchanged, is replaced by a non-infectious needle.

Al-Fwzan's model allowed for dividing the PWIDs population of type i into those PWIDs susceptible to HCV infection through needle and syringe sharing (denoted x_i for those not previously infected and x_{1i} for those previously infected), those in the acute stage of HCV infection (h_{1i} and h_{2i}), those who have progressed to the chronic stage of HCV infection (y_i) and those immune to HCV reinfection (z_i). As in Corson's model, 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. A susceptible PWID of type i (either x_i or x_{1i}) once infected with HCV will pass to the acute stage of infection (either h_{1i} or h_{2i}). Then those PWIDs newly infected with HCV will pass to the acute stage h_{1i} with probability $(1-\delta)$. Therefore these PWIDs will either die, leave the sharing injecting population, or pass to the chronic infection and stay there until they either die or leave the sharing injecting population. The lasting proportion δ of newly infected type i infected PWIDs pass to the acute h_{2i} stage. So these PWIDs will either die, leave the sharing injecting population or progress. Of those that progress a fraction α pass to the immune stage, where they will stay until they either die or leave the sharing injecting population. The other fraction $(1-\alpha)$ of those who progress from the h_{2i} stage return to the susceptible class.

Similarly, the shooting galleries are divided into q groups labeled $j = 1, 2, ...q$. Each shooting gallery j contains three different types of infectious needles. The only way that a type i PWID can be infected is through the sharing of needles used by an

HCV acutely or chronically infected PWID. Moreover, the infectivity of each needle is determined by the last infected PWID that it had come into contact with. Unused needles are uninfectious. Also, in this model Al-Fwzan and Greenhalgh (2015) assumed that the population of PWIDs is of size n where n is large and constant. Therefore, when PWIDs leave the population (due to either permanent cessation of injecting behaviour or death) at a per capita rate μ, they are immediately replaced by PWIDs susceptible to HCV infection.

Al-Fwzan and Greenhalgh (2015) derived a system of nine differential equations, six of them describe the transmission of HCV among PWIDs and three describe HCV prevalence in needles.

$$\frac{d\pi_{x_i}}{dt} = \mu - \mu\pi_{x_i} - \pi_{x_i}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}}+\beta_{h_{2j}})+\alpha_y\beta_{y_j}\big),$$

$$\frac{d\pi_{x_{1i}}}{dt} = \sigma(1-\alpha)\pi_{h_{2i}} - \mu\pi_{x_{1i}} - \pi_{x_{1i}}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}}+\beta_{h_{2j}})+\alpha_y\beta_{y_j}\big),$$

$$\frac{d\pi_{h_{1i}}}{dt} = \sum_{j=1}^{q}(1-\delta)(\pi_{x_i}+\pi_{x_{1i}})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}}+\beta_{h_{2j}})+\alpha_y\beta_{y_j}\big) - (\mu+\sigma)\pi_{h_{1i}},$$

$$\frac{d\pi_{h_{2i}}}{dt} = \sum_{j=1}^{q}\delta(\pi_{x_i}+\pi_{x_{1i}})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}}+\beta_{h_{2j}})+\alpha_y\beta_{y_j}\big) - (\mu+\sigma)\pi_{h_{2i}},$$

$$\frac{d\pi_{y_i}}{dt} = \sigma\pi_{h_{1i}} - \mu\pi_{y_i},$$

$$\frac{d\pi_{z_i}}{dt} = \sigma\alpha\pi_{h_{2i}} - \mu\pi_{z_i},$$

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

$$\frac{d\beta_{h_{2j}}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}}(1-\beta_{h_{2j}}) - \beta_{h_{2j}}\sum_{i=1}^{p}\Lambda_{ij}(1-\pi_{h_{2i}}) - \tau_j\beta_{h_{2j}},$$

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

The definitions of the model parameters are presented in Table 1.4. Define that R_0 is the key parameter to determine the behaviour of the model. Al-Fwzan and Greenhalgh (2015) derived the matrix $\boldsymbol{Q}_{ik}$ where:

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

Parameter	Description
ϕ_{ij}	Probability that a PWID in group i cleans a needle in shooting gallery j before use, $i = 1, 2, \ldots p$, $j = 1, 2, \ldots q$.
λ_i	Needle and syringe sharing rate in group i, $i = 1, 2, \ldots p$.
τ_j	Needle turnover rate in shooting gallery j.
μ	Per capita rate at which PWIDs leave the sharing, injecting population.
α_h	Acute HCV transmission probability.
α_y	Chronic HCV transmission probability.
$1/\sigma$	Duration of the acute HCV phase.
δ	Proportion of acutely infected PWIDs who resolve HCV infection.
α	Proportion of PWIDs that become immune.
P_{ij}	The probability that a PWID in group i chooses shooting gallery j to share a needle.
m_j	Number of needles in shooting gallery j.

Table 1.4: Table of Al-Fwzan and Greenhalgh (2015) model parameters definition.

where $\xi = (\alpha_y\sigma(1-\delta) + \alpha_h\mu)/\mu(\mu+\sigma)$. They have expected that the basic reproduction number R_0 to be the largest eigenvalue of the $p \times p$ matrix $\boldsymbol{Q}$, with $\boldsymbol{Q}_{ik} \geq 0$ for $i, k = 1, 2, ..., p$. Recall that $\rho(\boldsymbol{Q})$ the spectral radius of $\boldsymbol{Q}$ is defined to be

$$\rho(\boldsymbol{Q}) = \max_{1 \leq i \leq p} |\lambda_i|$$

where $\lambda_1, \lambda_2, ..., \lambda_p$ are the eigenvalues of $\boldsymbol{Q}$.

The results of this model shown that if $R_0 \leq 1$ then the disease will always die out, that is the disease-free equilibrium is globally asymptotically stable. Moreover it was shown that if $R_0 > 1$ then there is a unique non-zero endemic equilibrium. Also when $R_0 > 1$ then the disease-free equilibrium is unstable.

1.12.5 The Model by Pitcher et al. (2019)

The research article by Pitcher and his colleagues mainly focuses on mathematical modelling of the spread of HCV, especially based on the World Health Organization (WHO) targets, which are aimed at reducing HCV infection by 80% by 2030 across the globe. This article addresses treatment of HCV. Specifically, the article examines the insights offered by the models in relation to attaining WHO HCV targets, particularly concerning people who inject drugs (PWIDs). Importantly, based on the models, Pitcher et al. (2019) found that it is possible to eliminate HCV in various settings. However, focusing on harm reduction alone is not likely to attain the elimination target amongst PWIDs. The article also revealed that HCV testing and treatment that are used in many settings are not sufficient to eliminate the disease. Also, mathematical models are characterized by some uncertainties. For instance, they do not clearly indicate how the diagnosis and treatment of HCV impact behavioral change of affected persons.

The dynamic equations which describe the transmission of HCV in figure 1.6 are given by:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \theta - \pi(1-\delta)\frac{C+Z}{N}S + \omega\alpha T - \mu S,\\
\frac{dC(t)}{dt} &= \pi(1-\delta)\frac{C+Z}{N}S - f(C) - \mu C,\\
\frac{dT(t)}{dt} &= f(C) - \omega T - \mu T,\\
\frac{dZ(t)}{dt} &= \omega(1-\alpha)T - \mu Z,
\end{aligned}$$

where $S(t)$ refers to those uninfected, $C(t)$ refers to those chronic with HCV, $T(t)$ refers to those successfully treated and $Z(t)$ refers to those who failed treatment. Moreover, the total population is represented by $N(t)$ that means $N(t) = S(t) + C(t) + T(t) + Z(t)$.

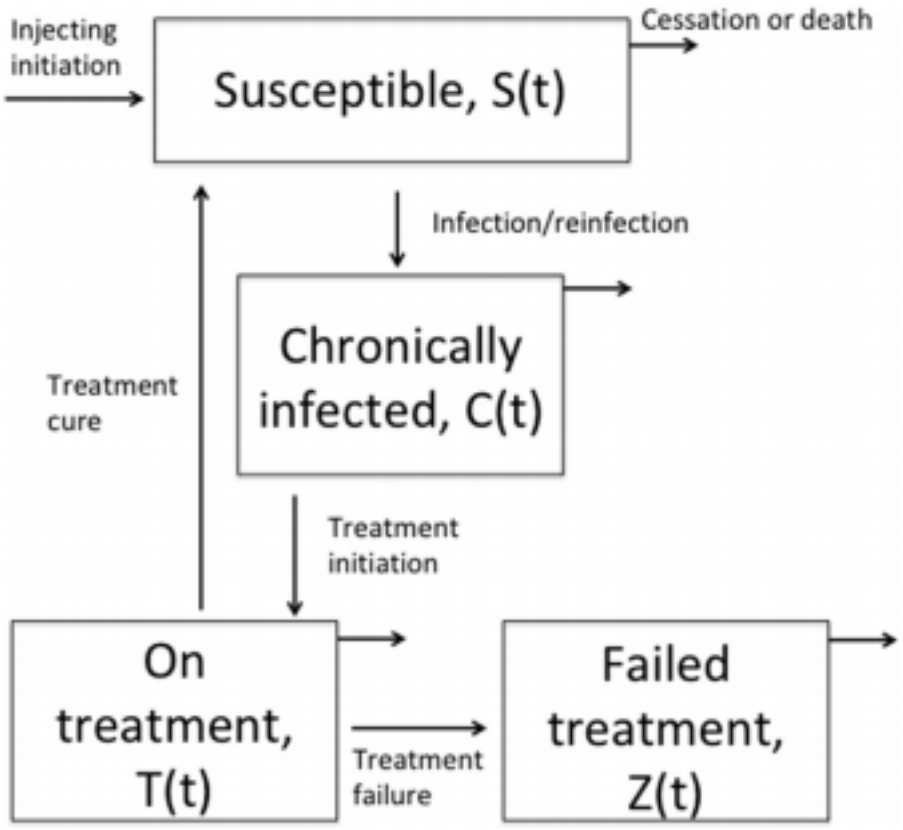

Figure 1.6: Simple digram of HCV transmission model among PWIDs (taken from Pitcher et al. (2019)).

Also θ, μ, π, δ, α and $1/\omega$ and $f(c)$ refer respectively to a fixed rate for PWIDs who enter the population, the infection rate, the per capita death rate, the proportion of those infected who self cure and become susceptible again, the period of time that a PWID who is being treated remains on treatment and a function $f(c)$ of PWIDs who can be treated.

Even though HCV is one of the main diseases that are killing millions of people globally, especially the PWID population, the models that examine the elimination of HCV are lacking in developing countries. The majority of models are utilized in the developed world like the USA, Europe, and Australia. The developing world, therefore, is lagging behind in the drive to eliminate HCV. The PWID population remains to be the group that is highly vulnerable to HCV infections. Pitcher et al. (2019) estimate that nearly 52% of PWIDs have been infected by HCV. As a result, the WHO elimination target is most likely to be achieved when it mainly focuses on

PWIDs. The article concludes that mathematical epidemic modeling plays a major role in eliminating HCV globally.

1.13 Conclusion

This opening chapter has presented an examination of literature relating to the epidemiology and modelling of HCV which is a major health issue transmitted through blood contact between an infectious individual and someone who is susceptible to the disease. HCV has a global impact, affecting millions. Up to four million new cases arise each year, of which the majority of those infected develop chronic HCV which is linked to severe liver disease (Seef (2002) and Kamal (2008)).

Much of this review and the models under study have looked at forecasting of the use of intervention methods in reducing the prevalence of HIV and HCV amongst PWIDs. In Scotland it has been recognised by the Scottish Parliament that the high levels of HCV which exist amongst PWIDs posed a serious public health risk which required substantial resources to be allocated in order that intervention methods could be improved and implemented to prevent HCV being transmitted (Scottish Executive (2011)). Resources can be allocated to the development and use of mathematical models including and similar to those reviewed in this study.

These models provide an insight into how infectious diseases, such as HIV and HCV spread and allow knowledge to be gained for various intervention measures to be evaluated as well as highlight the steps that are required for infectious disease to be eradicated. As has been seen in this review, various model structures exist, including deterministic, stochastic, SIS and SIR models. As the spread of HCV replicates that of HIV, those models and techniques which have been developed for the latter can also be applied to HCV models which examine the spread of disease amongst PWIDs.

Chapter 2

A Simple Pessimistic Model for the Spread of HCV Amongst PWIDs

Mathematical modelling techniques are now being used by health organizations worldwide to help understand the likely impact that intervention strategies, treatment options and combinations of these have on the prevalence and incidence of the hepatitis C virus (HCV) in the people who inject drugs (PWIDs) population. In this chapter, we develop a deterministic compartmental model for HCV transmission among PWIDs through the sharing of needles and syringes. Using analytical techniques, the model behaviour is governed by the basic reproduction number R_0, with R_0=1 being a critical threshold separating two different outcomes. It has been shown that if $R_0 \leq 1$ there is only the disease-free equilibrium whereas if $R_0 > 1$ there is the disease-free equilibrium and a unique endemic equilibrium. This model has a unique disease-free equilibrium which is globally stable if $R_0 \leq 1$. If $R_0 > 1$ the disease-free equilibrium is unstable. After that we look at a simplified approximate model by using the fact that the timescale on which injections take place is much faster than the timescale of epidemiological change. This approximation model has the same equilibria as the full model. Also, as Corson (2011) and Corson et al. (2012) we showed that if $R_0 > 1$ the endemic equilibrium is locally asymptotically

stable for our approximate model. A brief summary of the main findings concludes the chapter.

2.1 Model description

We develop a deterministic compartmental model for HCV transmission among PWIDs through the sharing of needles and syringes. The model was loosely based on the model previously described by Corson et al (2012). The treatment of chronically infected PWIDs is considered in the model. Recall that in the 'Optimistic Model' HIV transmission model amongst PWIDs studied by Greenhalgh and Lewis (2000) PWIDs were divided into 'Acute', 'Asymptomatic' and 'Pre-AIDS' groups according to their infectious disease status and needles were divided into the same groups according to the level of virus in the blood in the needle. The needles were supposed to adopt the infectious characteristics of the last PWID to use them, so a needle last used by a PWID in the Pre-AIDS stage would be in the Pre-AIDS class and a needle last used by a susceptible PWID would be left uninfected. This corresponds to the flushing assumption that PWIDs can rid a syringe of infectious blood made by Kaplan (1989). The model is called 'Optimistic' because needles adopt the infectious state of the last PWID to use them. This results in lower levels of HCV infection.

However in the 'Pessimistic Model' of HIV transmission amongst PWIDs studied by Lewis and Greenhalgh (2001a) the PWIDs and needles are divided into the same infectious classes but instead it is assumed that a needle used by a PWID adopts the most infectious state of its previous state and the infectious state of the PWID who last used it. Thus needles become progressively more infectious over time. This is based on the observation by Kaplan that HIV can be isolated from syringes even at great dilutions.

The model of the spread of HCV amongst PWIDs studied by Corson et al. (2012) is similar to the 'Optimistic Model' of Greenhalgh and Lewis (2000). We shall base our model on the model of Corson (2011) and Corson et al. (2012) but adopt the pessimistic needle mixing assumptions of Lewis and Greenhalgh (2001a), namely that needles adopt the most infectious of the current infectious state and

the state of the last infectious PWID to use them.

For instance, suppose that an acute phase h_1 infectious needle is also utilized by a PWID who is in the chronic y phase of infection. In this case, the needle remains in the acute h_1 infection phase. Conversely, if a needle that is in the chronic y phase of infection is utilized by an individual under the category of acute h_1 stage of infection then this needle will remain in the acute h_1 phase of infection. This assumption agrees with that made by Lewis and Greenhalgh (2001a) and results in this model being pessimistic in contrast to other possible assumptions and so we expect that it could be utilized to find a lower bound for the fraction of PWIDs and needles infected with HCV.

The parameters ϕ, λ, γ, μ, α_h, α_y, σ, δ and α are still similar to the definition in Corson's model (see Table 1.3). Also, we suppose a needle turnover rate of τ per year. Besides, we assume that infectious needles retain their infectivity even when they remain unused. Chronically infected individual PWIDs can be treated with antiviral therapy which is successful over 95% of the time (Chen et al. (2014)) and Cousien et al. (2018)) although successfully treated individual PWIDs can catch HCV again. Cousien et al. (2018) used a dynamic agent-based model of transmission amongst PWIDs to study optimal interventions to best manage HCV amongst PWIDs in France, in order to eliminate HCV. They take the new DAAs into consideration. Jia et al. (2019) consider a mathematical model for hepatitis C in China. Infected individuals are divided into acute and chronically infected. After the acute stage individuals can progress to the chronic, immune or treated stages (see Figure 2.1). We assume that the per capita rate at which chronically infected individual PWIDs are successfully treated is ψ.

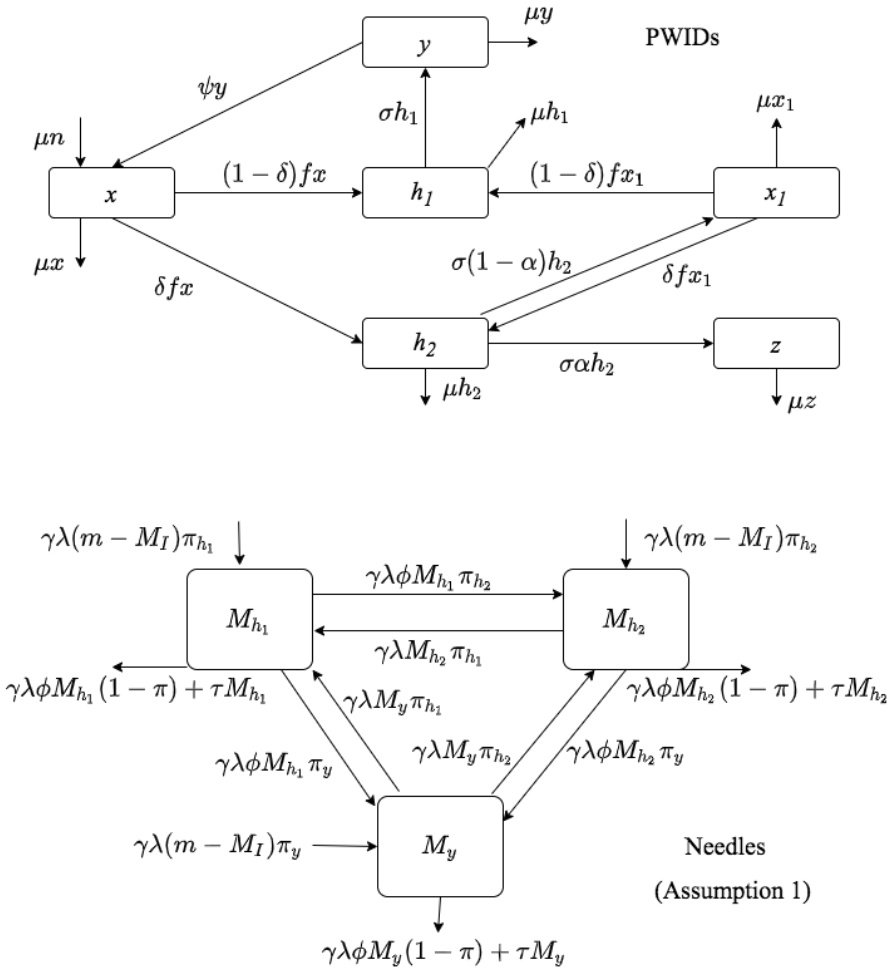

Figure 2.1: Our simple diagrams of our HCV transmission model among PWIDs.

2.1.1 Dynamic equations

We now start by deriving the differential equations which represent the spread of HCV among PWIDs where PWIDs progress through the different classes of HCV infection represented in the previous section and HCV infection is caused by sharing the three types of infectious needle described also in the previous section 2.1. We derive a total of eleven equations: six equations for PWIDs and five for needles for two assumptions in stages h_1 and h_2. For needles we have two alternative assumptions for how needles in state h_1 and h_2 interact, Assumption 1 and Assumption 2. Assumption 1 means that we regard state h_1 infectious needles as being slightly more infectious than state h_2 infectious needles and after use the level of infectivity

of a needle originally in state h_1 or state h_2 infectivity is the highest of its state immediately before use and the level of infectivity in the blood of PWID who last used it (as in Lewis and Greenhalgh (2001a)). Assumption 2 means that we regard state h_1 infectious needles and state h_2 infectious needles as being equally infectious and assume that a needle remains uninfectious until first used then adopts the infectious state of the last PWID to use it (as in Corson (2011) and Corson et al. (2012)). For each assumption we derive a total of nine equations, six for PWIDs and three for needles. Note that Assumption 1 and Assumption 2 are concerned only with the interaction of state h_1 PWIDs and state h_2 needles and vice-versa.

The flow diagrams for the equations are given in Figure 2.1, where the top part is for numbers of PWIDs and the bottom part is for needles (Assumption 1). Both are given in terms of absolute numbers not fractions. In these figures $\pi = \pi_{h_1} + \pi_{h_2} + \pi_y$ is the total fraction of infectious PWIDs, $M_{h_1} = m\beta_{h_1}$, $M_{h_2} = m\beta_{h_2}$, $M_y = m\beta_y$ and $M_I = M_{h_1} + M_{h_2} + M_y$ are the number of infectious needles in infectious stages h_1, h_2 and y, and the total number of infectious needles respectively. For Assumption 2 the flow from M_{h_1} to M_{h_2} is $\lambda\gamma M_{h_1}\pi_{h_2}$, with the other flows remaining unchanged.

Let $x(t)$, $x_1(t)$, $h_1(t)$, $h_2(t)$, $y(t)$ and $z(t)$ denote the number of PWIDs in respectively the x-susceptible, x_1-susceptible, h_1 acute, h_2 acute, chronic y and immune z classes at time t. Let $M_{h_1}(t)$, $M_{h_2}(t)$ and $M_y(t)$ denote respectively the number of acute state h_1 infectious needles, acute state h_2 infectious needles and chronic state y infectious needles at number t. Consider $\pi_x(t)$, $\pi_{x_1}(t)$, $\pi_{h_1}(t)$, $\pi_{h_2}(t)$, $\pi_y(t)$, and $\pi_z(t)$ to represent the fraction of PWIDs respectively in the x-susceptible, x_1-susceptible, acute h_1, acute h_2, chronic y and immune z classes at time t. Also, $\beta_{h_1}(t)$, $\beta_{h_2}(t)$ and $\beta_y(t)$ respectively represent the fraction of HCV infectious needles in the h_1, h_2 and y stages at time t. As in Corson (2011) and Corson et al. (2012), we denote the constant PWIDs to needle ratio $\gamma = n/m$ to be the number of PWIDs per needle in the population. Each susceptible PWID injects at rate λ. The probability that he or she becomes infected at injection is

$$(1 - \phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y).$$

So the force of infection experienced by a single susceptible PWID is still similar to

Corson (2011) and Corson et al. (2012)

$$f = \lambda(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y).$$

The change in the number of x-susceptible individuals in the small time interval $[t, t+\triangle t)$

$$\begin{aligned} x(t+\triangle t) - x(t) &= \text{new susceptible PWIDs born in } [t, t+\triangle t) \\ &\quad - x\text{-susceptible PWIDs who leave the sharing, injecting} \\ &\quad \text{population in } [t, t+\triangle t) \\ &\quad - x\text{-susceptible PWIDs who become infected in } [t, t+\triangle t) \\ &\quad \text{after borrowing needles and syringes last used by acute } h_1 \\ &\quad \text{PWIDs in } [t, t+\triangle t) \\ &\quad + \text{the number of } y\text{-chronic PWIDs who successfully treat HCV} \\ &\quad \text{infection in } [t, t+\triangle t), \\ \\ &= \mu n\triangle t - \mu x\triangle t - \lambda x(1-\phi)\triangle t(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y) + \psi y\triangle t \\ &\quad + o(\triangle t). \end{aligned}$$

Here writing $f(\xi) = o(\xi)$ means $\frac{f(\xi)}{\xi} \to 0$ as $\xi \to 0$. So

$$\frac{x(t+\triangle t) - x(t)}{\triangle t} = \mu n - \mu x - \lambda x(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y) + \psi y + o(1).$$

Letting $\triangle t \to 0$ we deduce that

$$\frac{dx}{dt} = \mu n - \mu x - \lambda x(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y) + \psi y.$$

Dividing by n, and recalling that $\pi_x = \frac{x}{n}, \pi_y = \frac{y}{n}$.

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

The derivations of the equations for the x_1-susceptible, acute h_1 and acute h_2 classes are a similar way to Corson (2011) and Corson et al. (2012). These equations

are

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

The change in the number of y chronic infected PWIDs individuals in the small time $[t, t+\triangle t)$

$$y(t+\triangle t) - y(t) = \text{ new chronic } y \text{ PWIDs in } [t,t+\triangle t) \text{ who come from the acute } h_1 \text{ stage}$$
$$- \text{ number of chronic } y \text{ PWIDs who die in } [t,t+\triangle t)$$
$$- \text{the number of } y\text{-chronic PWIDs who successfully treat HCV infection in } [t,t+\triangle t).$$

$$= \sigma h_1\triangle t - \mu y\triangle t - \psi y\triangle t + o(\triangle t).$$

So we have that

$$\frac{y(t+\triangle t)-y(t)}{\Delta t} = \sigma h_1 - \mu y - \psi y + o(1).$$

Letting $\triangle t \to 0$ we deduce that

$$\frac{dy}{dt} = \sigma h_1 - \mu y - \psi y.$$

Dividing by n then we have

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

Similarly for immune z PWIDs we have

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

Note that we assume that all new recruits into the PWID community are susceptible. This is reasonable as recruits are drawn from the general population where the level of HCV incidence is low. Similar assumptions are made in Greenhalgh and Lewis (2000). For needles recall that both stage h_1 and stage h_2 infectious needles are equally infectious. We shall discuss two possible assumptions for how stage h_1 and stage h_2 infectious needles and stage h_1 and stage h_2 infectious PWIDs interact. The first (Assumption 1) corresponds to the pessimistic needle assumptions in Lewis and Greenhalgh (2001a) where state h_1 infectious needles are regarded as more infectious than state h_2 infectious needles. So needles only move up the spectrum: uninfectious, state y infectious, state h_2 infectious, then state h_1 infectious. Hence, we assume that a stage h_1 PWID will always leave needles in state h_1 infectivity. Also, a stage h_2 PWID will always leave state h_2, state y and uncontaminated needles in state h_2 infectivity. Moreover, a stage y PWID will always leave state y and uncontaminated needles in state y infectivity.

The change in the number of acute h_1 needles and syringes in the small time interval $[t, t + \triangle t)$
$M_{h_1}(t + \triangle t) - M_{h_1}(t)$

$$
\begin{aligned}
&= \text{ the number of non } h_1 \text{ needles and syringes used by } h_1 \\
&\quad \text{infected PWIDs in } [t, t + \triangle t) \\
&- \text{ the number of } h_1 \text{ needles and syringes cleaned and then} \\
&\quad \text{used by non } h_1 \text{ infected PWIDs in } [t, t + \triangle t) \\
&- \text{ the number of } h_1 \text{ needles exchanged in } [t, t + \triangle t). \\
&= n\lambda\left(\frac{m - M_{h_1}}{m}\right)\pi_{h_1}\triangle t - n\lambda\frac{M_{h_1}}{m}(1 - \pi_{h_1})\phi\triangle t - \tau M_{h_1}\triangle t + o(\triangle t).
\end{aligned}
$$

So dividing by Δt, then letting $\Delta t \to 0$, we deduce that

$$\frac{dM_{h_1}}{dt} = n\lambda\left(1 - \frac{M_{h_1}}{m}\right)\pi_{h_1} - n\lambda\frac{M_{h_1}}{m}(1 - \pi_{h_1})\phi - \tau M_{h_1} + o(1).$$

Dividing by m,

$$\frac{d\beta_{h_1}}{dt} = \gamma\lambda(1 - \beta_{h_1})\pi_{h_1} - \gamma\lambda\beta_{h_1}(1 - \pi_{h_1})\phi - \tau\beta_{h_1}.$$

The change in the number of acute h_2 needles and syringes in the small time interval $[t, t+\triangle t)$

$M_{h_2}(t+\triangle t) - M_{h_2}(t)$

$=$ the number of non acute h_1 and non acute h_2 needles and syringes used by acute h_2 infected PWIDs in $[t, t+\triangle t)$

$+$ the number of acute h_1 needles and syringes cleaned and then used by acute h_2 infected PWIDs in $[t, t+\triangle t)$

$-$ the number of acute h_2 needles and syringes used by acute h_1 infected PWIDs in $[t, t+\triangle t)$

$-$ the number of acute h_2 needles and syringes cleaned and then used by non acute h_1 and non acute h_2 infected PWIDs in $[t, t+\triangle t)$

$-$ the number of acute h_2 needles exchanged in $[t, t+\triangle t)$.

$$= n\lambda\left(\frac{m - M_{h_1} - M_{h_2}}{m}\right)\pi_{h_2}\triangle t + n\lambda\frac{M_{h_1}}{m}\pi_{h_2}\phi\triangle t - n\lambda\frac{M_{h_2}}{m}\pi_{h_1}\triangle t$$
$$- n\lambda\frac{M_{h_2}}{m}(1 - \pi_{h_1} - \pi_{h_2})\phi\triangle t - \tau M_{h_2}\triangle t + o(\triangle t).$$

Dividing by $\triangle t$, and letting $\triangle t \to 0$ then we deduce that

$$\frac{dM_{h_2}}{dt} = n\lambda\left(1 - \frac{M_{h_1}}{m} - \frac{M_{h_2}}{m}\right)\pi_{h_2} + n\lambda\frac{M_{h_1}}{m}\pi_{h_2}\phi - n\lambda\frac{M_{h_2}}{m}\pi_{h_1}$$
$$- n\lambda\frac{M_{h_2}}{m}(1 - \pi_{h_1} - \pi_{h_2})\phi - \tau M_{h_2}.$$

Dividing by m,

$$\frac{d\beta_{h_2}}{dt} = \gamma\lambda(1 - \beta_{h_1} - \beta_{h_2})\pi_{h_2} + \gamma\lambda\phi\beta_{h_1}\pi_{h_2} - \gamma\lambda\beta_{h_2}\pi_{h_1}$$
$$- \gamma\lambda\phi\beta_{h_2}(1 - \pi_{h_1} - \pi_{h_2}) - \tau\beta_{h_2}.$$

The second assumption (Assumption 2) for how infectious state h_1, h_2 needles interact with infectious stage h_1, h_2 PWIDs corresponds to the Optimistic Model assumptions in Greenhalgh and Lewis (2000). Thus whilst they are in the state h_1 or h_2 infectivity state h_1 and state h_2 infectious needles adopt the infectious state

of the last h_1 or h_2 infectious state PWID to use them. Hence, we assume that a stage h_1 PWID will always leave needles in state h_1 infectivity. Also, a stage h_2 PWID will always leave needles in state h_2 infectivity. Moreover, a stage y PWID will always leave state y and uncontaminated needles in state y infectivity.

The change in the number of acute h_1 needles and syringes individuals in the small time interval $[t, t + \triangle t)$
$M_{h_1}(t + \triangle t) - M_{h_1}(t)$

$$
\begin{aligned}
= \quad & \text{the number of non acute } h_1 \text{ needles and syringes} \\
& \text{used by acute } h_1 \text{ infected PWIDs in } [t, t + \triangle t) \\
- \quad & \text{the number of acute } h_1 \text{ needles and syringes} \\
& \text{used by acute } h_2 \text{ infected PWIDs in } [t, t + \triangle t) \\
- \quad & \text{the number of acute } h_1 \text{ needles and syringes cleaned} \\
& \text{and then used by non acute } h_1 \text{ and non acute } h_2 \\
& \text{infected PWIDs in } [t, t + \triangle t) \\
- \quad & \text{the number of acute } h_1 \text{ needles exchanged in } [t, t + \triangle t).
\end{aligned}
$$

$$
\begin{aligned}
= \quad & n\lambda\left(\frac{m - M_{h_1}}{m}\right)\pi_{h_1}\triangle t - n\lambda\frac{M_{h_1}}{m}\pi_{h_2}\triangle t \\
& -n\lambda\phi\frac{M_{h_1}}{m}(1 - \pi_{h_1} - \pi_{h_2})\triangle t - \tau M_{h_1}\triangle t + o(\triangle t).
\end{aligned}
$$

Dividing by $\triangle t$, and letting $\triangle t \to 0$ then we deduce that

$$\frac{dM_{h_1}}{dt} = n\lambda\left(1 - \frac{M_{h_1}}{m}\right)\pi_{h_1} - n\lambda\frac{M_{h_1}}{m}\pi_{h_2} - n\lambda\phi\frac{M_{h_1}}{m}(1 - \pi_{h_1} - \pi_{h_2}) - \tau M_{h_1}.$$

Dividing by m,

$$\frac{d\beta_{h_1}}{dt} = \gamma\lambda(1 - \beta_{h_1})\pi_{h_1} - \gamma\lambda\beta_{h_1}\pi_{h_2} - \gamma\lambda\phi\beta_{h_1}(1 - \pi_{h_1} - \pi_{h_2}) - \tau\beta_{h_1}.$$

The change in the number of acute h_2 needles and syringes individuals in the small time interval $[t, t + \triangle t)$

$M_{h_2}(t+\triangle t) - M_{h_2}(t)$

$=$ the number of non acute h_2 needles and syringes used by acute h_2 infected PWIDs in $[t, t+\triangle t)$

$-$ the number of acute h_2 needles and syringes used by acute h_1 infected PWIDs in $[t, t+\triangle t)$

$-$ the number of acute h_2 needles and syringes cleaned and then used by non acute h_1 and non acute h_2 infected PWIDs in $[t, t+\triangle t)$

$-$ the number of acute h_2 needles exchanged in $[t, t+\triangle t)$.

$$= n\lambda\left(\frac{m - M_{h_2}}{m}\right)\pi_{h_2}\triangle t - n\lambda\frac{M_{h_2}}{m}\pi_{h_1}\triangle t - n\lambda\phi\frac{M_{h_2}}{m}(1 - \pi_{h_1} - \pi_{h_2})\triangle t - \tau M_{h_2}\triangle t + o(\triangle t).$$

Dividing by $\triangle t$, and letting $\triangle t \to 0$ then we deduce that

$$\frac{dM_{h_2}}{dt} = n\lambda\left(1 - \frac{M_{h_2}}{m}\right)\pi_{h_2} - n\lambda\frac{M_{h_2}}{m}\pi_{h_1} - n\lambda\phi\frac{M_{h_2}}{m}(1 - \pi_{h_1} - \pi_{h_2}) - \tau M_{h_2}.$$

Dividing by m,

$$\frac{d\beta_{h_2}}{dt} = \gamma\lambda(1 - \beta_{h_2})\pi_{h_2} - \gamma\lambda\beta_{h_2}\pi_{h_1} - \gamma\lambda\phi\beta_{h_2}(1 - \pi_{h_1} - \pi_{h_2}) - \tau\beta_{h_2}.$$

In both Assumption 1 and Assumption 2 infectious state h_1 or h_2 infectious needles are both more infectious than infectious state y infectious needles so in both cases the differential equation for infectious state y infectious needles is derived as follows:

The change in the number of chronic y needles and syringes in $[t, t+\triangle t)$ is $M_y(t+\triangle t) - M_y(t)$

$=$ the number of initially uninfected needles and syringes used by stage chronic y infected PWIDs in $[t, t+\triangle t)$

+ the number of initially acute h_1 or acute h_2 infected needles cleaned and used by chronic y infected PWIDs in $[t, t+\triangle t)$
− the number of initially chronic y infected needles used by acute h_1 or acute h_2 infected PWIDs in $[t, t+\triangle t)$
− the number of initially chronic y infected needles cleaned and used by susceptible PWIDs in $[t, t+\triangle t)$
− the number of chronic y needles exchanged in $[t, t+\triangle t)$.

$$= n\lambda\left(\frac{m - M_{h_1} - M_{h_2} - M_y}{m}\right)\pi_y\triangle t + n\lambda\phi\left(\frac{M_{h_1} + M_{h_2}}{m}\right)\pi_y\triangle t$$
$$- n\lambda\frac{M_y}{m}(\pi_{h_1} + \pi_{h_2})\triangle t - n\lambda\phi\frac{M_y}{m}(1 - \pi_{h_1} - \pi_{h_2} - \pi_y)\triangle t - \tau M_y\triangle t + o(\triangle t).$$

Dividing by $\triangle t$, and letting $\triangle t \to 0$ then we deduce that

$$\begin{aligned}\frac{dM_y}{dt} &= n\lambda\left(1 - \frac{M_{h_1}}{m} - \frac{M_{h_2}}{m} - \frac{M_y}{m}\right)\pi_y + n\lambda\phi\left(\frac{M_{h_1}}{m} + \frac{M_{h_2}}{m}\right)\pi_y \\ &\quad -n\lambda\frac{M_y}{m}(\pi_{h_1} + \pi_{h_2}) - n\lambda\phi\frac{M_y}{m}(1 - \pi_{h_1} - \pi_{h_2} - \pi_y) - \tau M_y.\end{aligned}$$

Dividing by m,

$$\begin{aligned}\frac{d\beta_y}{dt} &= \gamma\lambda(1 - \beta_{h_1} - \beta_{h_2} - \beta_y)\pi_y + \gamma\lambda\phi(\beta_{h_1} + \beta_{h_2})\pi_y - \gamma\lambda\beta_y(\pi_{h_1} + \pi_{h_2}) \\ &\quad -\lambda\gamma\phi\beta_y(1 - \pi_{h_1} - \pi_{h_2} - \pi_y) - \tau\beta_y.\end{aligned}$$

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

$$\frac{d\pi_x}{dt} = \mu - \mu\pi_x - \lambda\pi_x(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y) + \psi\pi_y, \tag{2.1.1}$$
$$\frac{d\pi_{x_1}}{dt} = \sigma(1-\alpha)\pi_{h_2} - \mu\pi_{x_1} - \lambda\pi_{x_1}(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y), \tag{2.1.2}$$
$$\begin{aligned}\frac{d\pi_{h_1}}{dt} &= (1-\delta)\lambda(1-\phi)(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y)(1 - \pi_{h_1} - \pi_{h_2} - \pi_y - \pi_z) \\ &\quad - (\mu + \sigma)\pi_{h_1},\end{aligned} \tag{2.1.3}$$
$$\begin{aligned}\frac{d\pi_{h_2}}{dt} &= \lambda(1-\phi)\delta(\alpha_h(\beta_{h_1} + \beta_{h_2}) + \alpha_y\beta_y)(1 - \pi_{h_1} - \pi_{h_2} - \pi_y - \pi_z) \\ &\quad - (\mu + \sigma)\pi_{h_2},\end{aligned} \tag{2.1.4}$$

$$\frac{d\pi_y}{dt} = \sigma\pi_{h_1} - \mu\pi_y - \psi\pi_y, \tag{2.1.5}$$
$$\frac{d\pi_z}{dt} = \sigma\alpha\pi_{h_2} - \mu\pi_z. \tag{2.1.6}$$

Under Assumption 1 for needles,

$$\frac{d\beta_{h_1}}{dt} = \gamma\lambda(1-\beta_{h_1})\pi_{h_1} - \gamma\lambda\beta_{h_1}(1-\pi_{h_1})\phi - \tau\beta_{h_1}, \tag{2.1.7}$$
$$\begin{aligned}\frac{d\beta_{h_2}}{dt} &= \gamma\lambda(1-\beta_{h_1}-\beta_{h_2})\pi_{h_2} + \gamma\lambda\phi\beta_{h_1}\pi_{h_2} - \gamma\lambda\beta_{h_2}\pi_{h_1} \\ &\quad - \gamma\lambda\phi\beta_{h_2}(1-\pi_{h_1}-\pi_{h_2}) - \tau\beta_{h_2}.\end{aligned} \tag{2.1.8}$$

Under Assumption 2 for needles,

$$\begin{aligned}\frac{d\beta_{h_1}}{dt} &= \gamma\lambda(1-\beta_{h_1})\pi_{h_1} - \gamma\lambda\beta_{h_1}\pi_{h_2} - \gamma\lambda\phi\beta_{h_1}(1-\pi_{h_1}-\pi_{h_2}) \\ &\quad - \tau\beta_{h_1},\end{aligned} \tag{2.1.9}$$
$$\begin{aligned}\frac{d\beta_{h_2}}{dt} &= \gamma\lambda(1-\beta_{h_2})\pi_{h_2} - \gamma\lambda\beta_{h_2}\pi_{h_1} - \gamma\lambda\phi\beta_{h_2}(1-\pi_{h_1}-\pi_{h_2}) \\ &\quad - \tau\beta_{h_2}.\end{aligned} \tag{2.1.10}$$

For both Assumptions we have that

$$\begin{aligned}\frac{d\beta_y}{dt} &= \gamma\lambda(1-\beta_{h_1}-\beta_{h_2}-\beta_y)\pi_y + \gamma\lambda\phi(\beta_{h_1}+\beta_{h_2})\pi_y - \gamma\lambda\beta_y(\pi_{h_1}+\pi_{h_2}) \\ &\quad - \lambda\gamma\phi\beta_y(1-\pi_{h_1}-\pi_{h_2}-\pi_y) - \tau\beta_y.\end{aligned} \tag{2.1.11}$$

Equations (2.1.1)-(2.1.6) represent how the PWIDs move through the different stages whereas (2.1.7)-(2.1.11) represent how the needles move through the different infectious stages.

For either assumption the initial conditions are $\pi_x(0) \geq 0$, $\pi_{x_1}(0) \geq 0$, $\pi_{h_1}(0) \geq 0$, $\pi_{h_2}(0) \geq 0$, $\pi_y(0) \geq 0$ and $\pi_z(0) \geq 0$; $\beta_{h_1}(0) \geq 0$, $\beta_{h_2}(0) \geq 0$ and $\beta_y(0) \geq 0$ with $\pi_x(0) + \pi_{x_1}(0) + \pi_{h_1}(0) + \pi_{h_2}(0) + \pi_y(0) + \pi_z(0) = 1$ and $\beta_{h_1}(0) + \beta_{h_2}(0) + \beta_y(0) < 1$.

2.2 Difference to Corson's model

The model of Corson (2011) also discussed in Corson et al. (2012) assumes that after use by an infected PWID each needle takes on the infectious state of the last PWID

to use it. However there is evidence from HIV that once infected needles remain permanently infected. Hence the assumption that the needle adopts the infectious state of the last PWID to use it may not be realistic and alternative assumptions must be explored. Here we have used two alternative assumptions which assume that the infectious state of the needle can only increase during its lifetime. The difference between the model discussed in Corson (2011) and Corson et al. (2012) is similar to the difference between models for the spread of HIV of Greenhalgh and Lewis (2000) who use an 'optimistic assumption' similar to Corson's model and that of Lewis and Greenhalgh (2001) who use a 'pessimistic assumption' similar to our model. Thus the PWID-needle interactions are more complicated in our models than those in Corson (2011) and Corson et al. (2012). As well as the different PWID needle interaction assumptions in our model addicts can also be treated at per capita rate ψ.

This completes our derivation of the basic model. In the next section we shall focus on a key epidemiological parameter, the basic reproduction number R_0.

2.3 The basic reproduction number R_0

The basic reproduction number is defined as the number of secondary infections caused by a single infectious person coming into a disease-free population at equilibrium (Corson (2011), Corson et al. (2012) and Al-Fwzan (2015)). A secondary infection is when someone is infected after using an infectious needle, contaminated by the originally infected PWID. In our model an alternative definition of R_0 is defined as the expected number of secondary needles infected by a single infected needle entering a disease-free population at equilibrium. A secondary needle infection is a needle infected by a PWID who was infected from the original infectious needle. R_0 is critically important in epidemiological models with the disease usually being eliminated when $R_0 < 1$ and an epidemic usually occurring when $R_0 > 1$. In unusual cases, usually in models with two or more different types of individuals, there may be subcritical endemic equilibria so disease can persist if $R_0 < 1$ (Greenhalgh et al. (2000)). To derive an expression for R_0 we note that for a single

newly infected PWID entering a population containing only susceptible PWIDs and uninfectious needles at the disease-free equilibrium, the initial infection process can be broken down into two distinct phases. Firstly the disease passes from our single infectious PWID to an uninfectious needle, secondly this needle (which is now infectious) passes on the disease to a susceptible PWID. We wish to find the expected number of needles a single PWID will infect during his or her infectious lifetime and the expected number of PWIDs each of these needles will infect. The product of these expected values is R_0. This results in a different value for R_0 than using the next generation matrix method although the threshold value is the same.

PWIDs progress through different infectious stages and during each stage a PWID will leave needles infectious. Following a similar way as in Corson (2011) and Corson et al. (2012) then we have on average a PWID generates

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

acute h_1 infectious needles and

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

acute h_2 infectious needles and

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

chronic y infectious needles.

We now want to find E_i(PWIDs infected by the single needle), where $i = h_1, h_2, y$ classes. Hence, we first define that:

$Y =$ the number of PWIDs infected by a single needle,

$X_1 =$ the event that the needle is safe before the next injection

and

$X_2 =$ the event that the needle is still infectious before the next injection.

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 is safe before the next injection that means $E_{h_1}(Y|X_1) = 0$ and if the needle is still infectious before the next injection then the probability of 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 explore $E_{h_1}(Y|X_2)$ by conditioning on the next event, that of a susceptible PWID injecting with an infectious needle. This event has two outcomes. A PWID may be infected by the needle or still remain susceptible. (Note that in this situation the needle is never flushed and this is different to the models discussed in Corson (2011) and Corson et al. (2012) where the needle is always flushed.) Consider the event that a susceptible PWID injects with an infectious needle, each of the two outcomes mentioned previously are possible and each outcome has different implications for the number of PWIDs infected by this needle. If the PWID becomes infected then the number of PWIDs infected from the needle before the next injection is one, if the PWID is not infected then the number of PWIDs infected from the needle before the next injection is zero. In the case the needle infects the susceptible PWID then it will infect in total $E_{h_1}+1$ PWIDs where $E_{h_1} = E_{h_1}$ (PWIDs infected by a single needle), similarly if the PWID was not infected then the needle will infect in total E_{h_1} PWIDs.

Hence, we are assuming that a susceptible PWID always leaves an infectious needle in the infectious state that means an infectious needle is never flushed by a susceptible PWID. Namely that the PWID is infected by the needle with probability α_h or remains susceptible with probability $1-\alpha_h$. Therefore,

$$E_{h_1} = \frac{\lambda\gamma(1-\phi)}{\lambda\gamma+\tau}\Big[\mathrm{P}(\text{susceptible PWID infected}) + \mathrm{P}(\text{needle not flushed})E_{h_1}\Big]. \tag{2.3.12}$$

Here P(needle not flushed) =1. This is different to the models discussed in Corson (2011) and Corson et al. (2012) where in this situation P(needle not flushed) = 0.

Hence (2.3.12) is

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

Solving for E_{h_1} we deduce that

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

Here $\hat{\tau} = (\tau/\lambda\gamma)$.

A second way to derive E_{h_1} is to note that at each stage the needle remains infectious between PWIDs with probability

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

and infects a previously susceptible PWID with probability α_h at each injection. Hence the probability that the needle remains infectious for PWIDs $1, 2, 3, \ldots i-1$ but does not remain infectious for PWID i is

$$\left[1 - \frac{1-\phi}{1+\hat{\tau}}\right]\left(\frac{1-\phi}{1+\hat{\tau}}\right)^{i-1} = \frac{\phi+\hat{\tau}}{1+\hat{\tau}}\left(\frac{1-\phi}{1+\hat{\tau}}\right)^{i-1} \qquad i = 1, 2, 3, \ldots$$

in other words a geometric distribution with $p = \frac{1-\phi}{1+\hat{\tau}}$.

So the total number of PWIDs to use the needle and become infected before the needle becomes uninfectious is

$$S = E_{h_1} = \alpha_h \frac{\phi+\hat{\tau}}{1+\hat{\tau}}\left[0 + \frac{1(1-\phi)}{1+\hat{\tau}} + \frac{2(1-\phi)^2}{(1+\hat{\tau})^2} + \frac{3(1-\phi)^3}{(1+\hat{\tau})^3} + \ldots\right].$$

Multiplying by $\frac{1-\phi}{1+\hat{\tau}}$

$$S\frac{(1-\phi)}{1+\hat{\tau}} = \alpha_h \frac{(\phi+\hat{\tau})}{(1+\hat{\tau})}\left[0 + \frac{1(1-\phi)^2}{(1+\hat{\tau})^2} + \frac{2(1-\phi)^3}{(1+\hat{\tau})^3} + \frac{3(1-\phi)^4}{(1+\hat{\tau})^4} + \ldots\right].$$

Subtracting

$$\begin{aligned} S\frac{(\phi+\hat{\tau})}{1+\hat{\tau}} &= \alpha_h \frac{(\phi+\hat{\tau})}{1+\hat{\tau}}\left[\frac{(1-\phi)}{1+\hat{\tau}} + \frac{(1-\phi)^2}{(1+\hat{\tau})^2} + \frac{(1-\phi)^3}{(1+\hat{\tau})^3} + \ldots\right]. \\ &= \alpha_h \frac{(\phi+\hat{\tau})(1-\phi)}{(1+\hat{\tau})^2}\left[\frac{1}{1-\frac{1-\phi}{1+\hat{\tau}}}\right]. \\ &= \alpha_h \frac{(1-\phi)}{1+\hat{\tau}}. \end{aligned}$$

Hence

$$S = \alpha_h \frac{(1-\phi)}{\phi+\hat{\tau}}.$$

So

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

Moreover, this argument is the same in the acute h_2 and chronic y for Assumption 1 and Assumption 2 because in both assumptions we have assumed that the PWIDs never flushed needles. Therefore, we use a similar argument to derive the expected number of PWIDs that are infected by acute h_2 and chronic y needles in both assumptions of needles until they are uninfectious. These are

$$E_{h_2} = \frac{(1-\phi)\alpha_h}{\phi + \hat{\tau}}$$

and

$$E_y = \frac{(1-\phi)\alpha_y}{\phi + \hat{\tau}}$$

respectively.

An expression for the total of secondary infections caused by one infectious PWID entering the disease-free population can be calculated by multiplying the expected number of infections from each type of infectious needle (in both assumptions) with the expected number of needles that a PWID generates during their infectious lifetime. This gives

$$\frac{\lambda(1-\delta)}{(\mu+\sigma)}\frac{(1-\phi)\alpha_h}{(\phi+\hat{\tau})} + \frac{\lambda\delta}{(\mu+\sigma)}\frac{(1-\phi)\alpha_h}{(\phi+\hat{\tau})} + \frac{\lambda\sigma(1-\delta)}{(\mu+\psi)(\mu+\sigma)}\frac{(1-\phi)\alpha_y}{(\phi+\hat{\tau})}$$

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

Hence, the basic reproduction number is given by

$$R_0 = \frac{\lambda(1-\phi)}{(\mu+\psi)(\mu+\sigma)(\phi+\hat{\tau})}[(\mu+\psi)\alpha_h + \alpha_y\sigma(1-\delta)]. \tag{2.3.13}$$

Thus, we conclude that R_0 is the same for Assumption 1 and Assumption 2. Moreover it is different than R_0 in Corson (2011) and Corson et al. (2012) because of the ψ terms and also the factor $(\phi + \hat{\tau})$ in the denominator.

Another way to derive our R_0 is by considering R_0 as the number of HCV cases in PWIDs caused via exactly one infected syringe from a single newly infected PWID entering the DFE point (Liang et al. (2019), Macdonald (1952), Maier et al.

(2017), Massad et al. (2001), Sanches and Massad (2016) and Van den Driessche (2017)). An alternative approach (Diekmann et al. (1990), Roberts and Heesterbeek (2003), Van den Driessche (2017), Van den Driessche and Watmough (2002), Van den Driessche and Watmough (2008) and Wonham and Lewis (2008)) takes the interval between cases of disease to be between vector (in our case needles) and human (individual PWID) or human and vector. If this method is applied the new basic reproduction number, R_0^* say, is the unique positive real root of a cubic equation. As $R_0^* > 1$ if and only if $R_0 > 1$ and $R_0^* < 1$ if and only if $R_0 < 1$ this R_0^* has the same threshold value as R_0.

We work with the equations representing the absolute number of PWIDs and needles not the proportions. The infectious compartments are h_1, h_2, y and M_{h_1}, M_{h_2} and M_y.

$$\begin{aligned}
\frac{dh_1}{dt} &= \frac{\lambda}{m}(1-\delta)(1-\phi)\big[\alpha_h(M_{h_1}+M_{h_2})+\alpha_y M_y\big]\big(n-h_1-h_2-y-z\big) \\
&\quad -(\mu+\sigma)h_1, \\
\frac{dh_2}{dt} &= \frac{\lambda}{m}\delta(1-\phi)\big[\alpha_h(M_{h_1}+M_{h_2})+\alpha_y M_y\big]\big(n-h_1-h_2-y-z\big)-(\mu+\sigma)h_2, \\
\frac{dy}{dt} &= \sigma h_1-(\mu+\psi)y, \\
\frac{dM_{h_1}}{dt} &= \frac{\lambda}{m}(m-M_{h_1})h_1-\frac{\lambda}{m}M_{h_1}(n-h_1)\phi-\tau M_{h_1}, \\
\frac{dM_{h_2}}{dt} &= \frac{\lambda}{m}(m-M_{h_1}-M_{h_2})h_2+\frac{\lambda}{m}\phi M_{h_1}h_2-\frac{\lambda}{m}M_{h_2}h_1-\frac{\lambda}{m}\phi M_{h_2}(n-h_1-h_2) \\
&\quad -\tau M_{h_2}, \\
\frac{dM_y}{dt} &= \frac{\lambda}{m}(m-M_{h_1}-M_{h_2}-M_y)y+\frac{\lambda}{m}\phi(M_{h_1}+M_{h_2})y-\frac{\lambda}{m}M_y(h_1+h_2) \\
&\quad -\frac{\lambda}{m}\phi M_y(n-h_1-h_2-y)-\tau M_y.
\end{aligned}$$

Recall that F_i is the rate at which new cases of disease arise in the i'th class

$$
\begin{aligned}
F_1 &= (1-\delta)\frac{\lambda}{m}(1-\phi)\big(\alpha_h(M_{h_1}+M_{h_2})+\alpha_y M_y\big)(n-h_1-h_2-y-z),\\
F_2 &= \delta\frac{\lambda}{m}(1-\phi)\big(\alpha_h(M_{h_1}+M_{h_2})+\alpha_y M_y\big)(n-h_1-h_2-y-z),\\
F_3 &= \sigma h_1,\\
F_4 &= \frac{\lambda}{m}(m-M_{h_1})h_1,\\
F_5 &= \frac{\lambda}{m}(m-M_{h_1}-M_{h_2})h_2+\frac{\lambda}{m}\phi h_2 M_{h_1},\\
F_6 &= \frac{\lambda}{m}(m-M_{h_1}-M_{h_2}-M_y)y+\frac{\lambda}{m}\phi(M_{h_1}+M_{h_2})y.
\end{aligned}
$$

Hence recalling our discussion of the Next Generation Matrix Method in Section 1.4.1

$$
\boldsymbol{F}=\begin{vmatrix}
0 & 0 & 0 & (1-\delta)(1-\phi)\alpha_h\lambda\gamma & (1-\delta)(1-\phi)\alpha_h\lambda\gamma & (1-\delta)(1-\phi)\alpha_y\lambda\gamma\\
0 & 0 & 0 & \delta(1-\phi)\alpha_h\lambda\gamma & \delta(1-\phi)\alpha_h\lambda\gamma & \delta(1-\phi)\alpha_y\lambda\gamma\\
\sigma & 0 & 0 & 0 & 0 & 0\\
\lambda & 0 & 0 & 0 & 0 & 0\\
0 & \lambda & 0 & 0 & 0 & 0\\
0 & 0 & \lambda & 0 & 0 & 0
\end{vmatrix},
$$

$$\boldsymbol{V} = \begin{vmatrix} (\mu+\sigma) & 0 & 0 & 0 & 0 & 0 \\ 0 & (\mu+\sigma) & 0 & 0 & 0 & 0 \\ 0 & 0 & (\mu+\psi) & 0 & 0 & 0 \\ 0 & 0 & 0 & \lambda\gamma\phi+\tau & 0 & 0 \\ 0 & 0 & 0 & 0 & \lambda\gamma\phi+\tau & 0 \\ 0 & 0 & 0 & 0 & 0 & \lambda\gamma\phi+\tau \end{vmatrix}.$$

So calculating $\boldsymbol{FV}^{-1}$ gives the Next Generation Matrix and similarly for Assumption 2. Therefore, using the next generation matrix approach there are six types of infectious entities h_1, h_2 and y for individual PWIDs and M_{h_1}, M_{h_2} and M_y for needles. The next generation matrix is defined as the matrix $\boldsymbol{M} = \{M_{ij} : i = 1,2,3,4,5,6, j = 1,2,3,4,5,6\}$ where M_{ij} is defined as the expected number of secondary cases in infectious state i caused by a single newly infectious PWID in infectious state j entering a disease free population at equilibrium. Hence

$$\boldsymbol{M} = \begin{pmatrix} 0 & 0 & 0 & \alpha_h(1-\delta)\phi^* & \alpha_h(1-\delta)\phi^* & \alpha_y(1-\delta)\phi^* \\ 0 & 0 & 0 & \alpha_h\delta\phi^* & \alpha_h\delta\phi^* & \alpha_y\delta\phi^* \\ \dfrac{\sigma}{\mu+\sigma} & 0 & 0 & 0 & 0 & 0 \\ \dfrac{\lambda}{\mu+\sigma} & 0 & 0 & 0 & 0 & 0 \\ 0 & \dfrac{\lambda}{\mu+\sigma} & 0 & 0 & 0 & 0 \\ 0 & 0 & \dfrac{\lambda}{\mu+\psi} & 0 & 0 & 0 \end{pmatrix}$$

where $\phi^* = \frac{1-\phi}{\phi+\hat{\tau}}$. It is straightforward to show that three of the eigenvalues of this matrix are zero and the remaining three satisfy $f(\omega) = 0$ where

$$f(\omega) = \omega^3 - \alpha_h\phi^*\frac{\lambda}{\mu+\sigma}\omega - \alpha_y\phi^*\frac{\lambda\sigma(1-\delta)}{(\mu+\sigma)(\mu+\psi)}.$$

As $f(0) < 0$ and $\lim_{\omega\to\infty} f(\omega) = \infty$ the equation $f(\omega) = 0$ has either one or three strictly positive real roots. By Descartes rule of signs it has either zero or one strictly positive real roots (Bennett (1922)), hence has exactly one positive real root. Moreover as the Next Generation Matrix $\boldsymbol{M}$ is a positive irreducible matrix it has a real strictly positive eigenvalue corresponding to its spectral radius (Lemma 2.1 in Nold, 1980), which is R_0^*, the basic reproduction number by the Next Generation Matrix method. Moreover $f(1) = 1 - R_0$. Hence $R_0^* > 1$ if and only if $R_0 > 1$, $R_0^* = 1$ if and only if $R_0 = 1$, and $R_0^* < 1$ if and only if $R_0 < 1$. So R_0 and R_0^* have the same threshold value.

We now going to see the behaviour of our model analytically. In particular, in the conditions that allow HCV to die out or persist in the population.

2.4 Analytical results

In this section we are going to analyse the behaviour of our transmission model, centering on the conditions that result in HCV persistence or elimination. We proceed with an equilibrium and stability analysis in order to determine the nature of any equilibrium solutions. Then we shall show that there are two equilibrium solutions; a zero and an unique non-zero solution. Stability analysis will present that the zero solution is globally stable when $R_0 \leq 1$ and unstable when $R_0 > 1$. After that we will derive an approximation to our differential equation model with the same basic reproduction number and equilibria. The non-zero solution for our approximation model is locally asymptotically stable when $R_0 > 1$.

Moreover we will suppose 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 PWIDs do not engage in cleaning practices prior to injecting. In addition, we suppose that the remaining model parameters are

strictly positive.

2.4.1 Equilibrium solutions

Theorem 2.4.1. *In either system (2.1.1)-(2.1.8) and (2.1.11) or (2.1.1)-(2.1.6) and (2.1.9)-(2.1.11), if $R_0 \leq 1$ then the system has a unique equilibrium solution where the disease has died out in both PWIDs and needles and syringes. If $R_0 > 1$ then there is the DFE, moreover there is a unique endemic equilibrium point.*

Proof. If we are using the similar method which was used in proving of Theorem 3.1 in Corson (2011) and proving of Theorem 4.1 in Corson et al. (2012) and considering the different PWID needle interaction assumptions in our model addicts can also be treated at per capita rate ψ therefore we can write π_i^* and β_j^* where $i = x,\ x_1,\ h_1,\ h_2,\ y,\ z$ and $j = h_1,\ h_2,\ y$ represent to the endemic equilibrium proportions of PWIDs and needles respectively. Putting $\frac{d}{dt} = 0$ in equations (2.1.1)-(2.1.11) and then defining $\pi_{h_1}^* = (1-\delta)k$, which leads to $\pi_{h_2}^* = \delta k$ from (2.1.3) and (2.1.4), we have that

$$\pi_y^* = \frac{\sigma(1-\delta)k}{\mu+\psi} \quad , \quad \pi_z^* = \frac{\sigma\alpha\delta k}{\mu}.$$

For Assumption 1 we have that

$$\beta_{h_1}^* = \frac{(1-\delta)k}{(1-\delta)k(1-\phi)+\phi+\hat{\tau}} \qquad \text{and}$$
$$\beta_{h_2}^* = \frac{k\delta(\phi+\hat{\tau})}{(k(1-\phi)+\phi+\hat{\tau})(k(1-\delta)(1-\phi)+\phi+\hat{\tau})}.$$

For Assumption 2 we have that

$$\beta_{h_1}^* = \frac{k(1-\delta)}{k(1-\phi)+\phi+\hat{\tau}} \quad \text{and} \quad \beta_{h_2}^* = \frac{k\delta}{k(1-\phi)+\phi+\hat{\tau}}.$$

For notational simplicity write $\pi_h = \pi_{h_1} + \pi_{h_2}$, $\beta_h = \beta_{h_1} + \beta_{h_2}$, $\pi = \pi_{h_1} + \pi_{h_2} + \pi_y$ and $\beta = \beta_{h_1} + \beta_{h_2} + \beta_y$. Denote their respective equilibrium values by π_h^*, β_h^*, π^* and β^*. Then for both Assumption 1 and Assumption 2

$$\frac{d\beta_h}{dt} = \gamma\lambda(1-\beta_h)\pi_h - \gamma\lambda\phi\beta_h(1-\pi_h) - \tau\beta_h, \tag{2.4.14}$$

and

$$\frac{d\beta}{dt} = \gamma\lambda(1-\beta)\pi - \gamma\lambda\phi\beta(1-\pi) - \tau\beta. \tag{2.4.15}$$

Hence from the equilibrium versions of these equations

$$\beta_h^* = \frac{k}{k(1-\phi)+\phi+\hat{\tau}},$$
$$\beta^* = \frac{k\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}\right)}{k\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}\right)(1-\phi)+\phi+\hat{\tau}},$$

and

$$\beta_y^* = \frac{(\phi+\hat{\tau})\frac{\sigma k(1-\delta)}{\mu+\psi}}{\big(k(1-\phi)+\phi+\hat{\tau}\big)\big[k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat{\tau}\big]}.$$

Adding the equilibrium versions of equations (2.1.3) and (2.1.4) we deduce that

$$k = \pi_h^* = \frac{\lambda(1-\phi)}{\mu+\sigma}(1-\pi^*-\pi_z^*)\big((\alpha_h-\alpha_y)\beta_h^*+\alpha_y\beta^*\big).$$

Hence $k=$

$$\frac{\lambda(1-\phi)}{\mu+\sigma}\left(1-k\left[1+\frac{\sigma(1-\delta)}{\mu+\psi}+\frac{\sigma\alpha\delta}{\mu}\right]\right)\left(\frac{(\alpha_h-\alpha_y)k}{k(1-\phi)+\phi+\hat{\tau}} + \frac{k\alpha_y\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)}{k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)+\phi+\hat{\tau}}\right). \tag{2.4.16}$$

$k = 0$ is always a possible solution of (2.4.16) corresponding to the disease-free equilibrium solution which is therefore always possible. Any other non-zero solution must satisfy

$$1 = \frac{\lambda(1-\phi)}{\mu+\sigma}\left(1-k\left[1+\frac{\sigma(1-\delta)}{\mu+\psi}+\frac{\sigma\alpha\delta}{\mu}\right]\right)\left(\frac{(\alpha_h-\alpha_y)}{k(1-\phi)+\phi+\hat{\tau}} + \frac{\alpha_y\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)}{k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)+\phi+\hat{\tau}}\right). \tag{2.4.17}$$

Let $g(k)$ denote the right-hand side of (2.4.17). $g(k)$ is strictly monotone decreasing in k with $g(0) = R_0$. Hence if $R_0 \leq 1$ there are no strictly positive solutions to (2.4.17) whereas if $R_0 > 1$ there is a unique strictly positive solution to (2.4.17) in $(0, k^*)$ where $k^* = 1/[1 + (\sigma(1-\delta)/(\mu+\psi)) + (\sigma\alpha\delta/\mu)]$.

It is straightforward to show that this strictly positive solution corresponds to an endemic equilibrium for either Assumption 1 or Assumption 2. Hence we have shown that if $R_0 > 1$ there is a unique feasible endemic equilibrium with all of $\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*, \beta_{h_1}^*, \beta_{h_2}^*$ and β_y^* strictly positive and if $R_0 \leq 1$ there is only the disease-free equilibrium. □

We conclude that the proof of 2.4.1 is different to Corson (2011) and Corson et al. (2012). It is a more complicated and significantly different proof because of the needle equations. Also R_0 is the same for the Pessimistic Model with both Assumption 1 and Assumption 2. There is a difference between the results for Assumption 1 and Assumption 2 in that the $\beta_{h_1}^*$ and $\beta_{h_2}^*$ value differs.

2.4.2 Global stability of the disease free equilibrium

We are going now to see what happens when $0 \leq R_0 \leq 1$. In this situation we shall show that when R_0 takes the values between 0 and 1 inclusive HCV will die out in all PWIDs and needles and syringes.

Theorem 2.4.2. *If $R_0 \leq 1$ HCV will be eradicated in all PWIDs and needles and syringes.*

Proof. Note that the idea of the proof is similar to that of Corson (2011) and Corson (2012) but the main difference is the needle equations. There is also the PWID treatment rate ψ. This outcome is proved in several steps. We write $\pi_{h_1}^\infty$ for $\lim_{t\to\infty} \sup \pi_{h_1}(t)$, with similar definitions for the other π_i^∞ and β_j^∞ for $i = x_1,\ h_1,\ h_2,\ y,\ z$ and $j = h_1,\ h_2,\ y$. We start off proving several results that give upper bounds on the limit suprema of each PWID and needle class in terms of either $\pi_{h_1}^\infty$ or $\pi_{h_2}^\infty$, this leads us to express our results in terms of a single limit supremum. We then show if $R_0 \leq 1$ this limit supremum is equal to zero. Applying

this result will complete the proof.

Lemma 2.4.3. $\pi_y^\infty \leq \dfrac{\sigma\pi_{h_1}^\infty}{\mu+\psi}$.

Proof. From equation (2.1.5), we have that

$$\frac{d\pi_y}{dt} + (\mu+\psi)\pi_y = \sigma\pi_{h_1}.$$

To solve by using an integrating factor, we have

$$\frac{d}{dt}[\pi_y \exp((\mu+\psi)t)] = \sigma\pi_{h_1}\exp((\mu+\psi)t).$$

So given $\epsilon > 0$, there exists $t_1(\epsilon) \geq 0$ such that for $t \geq t_1(\epsilon)$

$$\frac{d}{dt}[\pi_y \exp((\mu+\psi)t)] \leq \sigma(\pi_{h_1}^\infty + \epsilon)\exp((\mu+\psi)t).$$

Let $t \geq t_1(\epsilon)$ and integrating over $[t_1(\epsilon), t]$ gives

$$\pi_y(t)\exp((\mu+\psi)t) - \pi_y(t_1(\epsilon))\exp((\mu+\psi)t_1(\epsilon)) \leq (\pi_{h_1}^\infty+\epsilon)\sigma\frac{1}{\mu+\psi}(\exp((\mu+\psi)t) - \exp((\mu+\psi)t_1(\epsilon))),$$

$$\begin{aligned}\pi_y(t) &\leq \pi_y(t_1(\epsilon))\exp(-(\mu+\psi)(t-t_1(\epsilon))) \\ &\quad + (\pi_{h_1}^\infty+\epsilon)\sigma\frac{1}{\mu+\psi}(1-\exp[-(\mu+\psi)(t-t_1(\epsilon))]), \\ &\leq \exp(-(\mu+\psi)(t-t_1(\epsilon))) + (\pi_{h_1}^\infty+\epsilon)\sigma\frac{1}{\mu+\psi}.\end{aligned}$$

Note there exists $t_2(\epsilon) > t_1(\epsilon)$ such that $\exp(-(\mu+\psi)(t-t_1(\epsilon))) \leq \epsilon$. For $t \geq t_2(\epsilon)$

$$\pi_y(t) \leq \epsilon + (\pi_{h_1}^\infty+\epsilon)\sigma\frac{1}{\mu+\psi} = \frac{\sigma\pi_{h_1}^\infty}{\mu+\psi} + \epsilon_1, \qquad \text{where } \epsilon_1 = \epsilon\left(\frac{\mu+\psi+\sigma}{\mu+\psi}\right).$$

Suppose that $\pi_y^\infty > \frac{\sigma\pi_{h_1}^\infty}{\mu+\psi}$. Then take $\epsilon_1 = \frac{1}{2}\left(\pi_y^\infty - \frac{\sigma\pi_{h_1}^\infty}{\mu+\psi}\right) > 0$. For $t \geq t_2(\epsilon)$,

$$\pi_y(t) \leq \frac{\sigma\pi_{h_1}^\infty}{\mu+\psi} + \frac{1}{2}\left(\pi_y^\infty - \frac{\sigma\pi_{h_1}^\infty}{\mu+\psi}\right).$$

Letting $t \to \infty$,

$$\pi_y^\infty \leq \frac{\sigma\pi_{h_1}^\infty}{2(\mu+\psi)} + \frac{1}{2}\pi_y^\infty.$$

Re-arranging we deduce that

$$\pi_y(t) \leq \frac{\sigma\pi_{h_1}^{\infty}}{\mu+\psi}.$$

This is a contradiction therefore $\pi_y(t) \leq \frac{\sigma\pi_{h_1}^{\infty}}{\mu+\psi}$, completing the proof. □

Corollary 2.4.1. $\pi_z^{\infty} \leq \frac{\sigma\alpha\pi_{h_2}^{\infty}}{\mu}$.

Proof.

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

Using the same method which was used in the proof of Lemma 2.4.3 the result follows. □

We shall next use the same method and equations (2.1.7)-(2.1.8) and (2.1.11) for Assumption 1 and equations (2.1.9)-(2.1.11) for Assumption 2 to find upper bounds for $\beta_{h_1}^{\infty}$, $\beta_{h_2}^{\infty}$ and β_y^{∞}. Recall that $\hat{\tau} = \frac{\tau}{\lambda\gamma}$. For Assumption 1 from equation (2.1.7) we have that

$$\frac{d\beta_{h_1}}{dt} = \gamma\lambda\pi_{h_1} - \gamma\lambda\beta_{h_1}(\phi+\hat{\tau}) - \gamma\lambda\pi_{h_1}\beta_{h_1}(1-\phi).$$

For Assumption 2 from equation (2.1.9) we have that

$$\frac{d\beta_{h_1}}{dt} = \gamma\lambda\pi_{h_1} - \gamma\lambda\beta_{h_1}(\phi+\hat{\tau}) - \gamma\lambda(\pi_{h_1}+\pi_{h_2})\beta_{h_1}(1-\phi).$$

So in both cases

$$\frac{d\beta_{h_1}}{dt} \leq \gamma\lambda\pi_{h_1} - \gamma\lambda\beta_{h_1}(\phi+\hat{\tau}).$$

So multiplying by $\exp\big(\lambda\gamma(\phi+\hat{\tau})t\big)$ we have

$$\frac{d}{dt}[\beta_{h_1}\exp(\lambda\gamma(\phi+\hat{\tau})t)] \leq \lambda\gamma\pi_{h_1}\exp(\lambda\gamma(\phi+\hat{\tau})t).$$

Proceeding as in the proof of Lemma 2.4.3 we deduce that

$$\beta_{h_1}^{\infty} \leq \frac{\pi_{h_1}^{\infty}}{\phi+\hat{\tau}}.$$

Similarly for β_{h_2} for Assumption 1 from equation (2.1.8) we have that

$$\begin{aligned}\frac{d\beta_{h_2}}{dt} &\leq \gamma\lambda\pi_{h_2} - \gamma\lambda\beta_{h_2}(\phi+\hat{\tau}) - \gamma\lambda(\pi_{h_1}+\pi_{h_2})\beta_{h_2}(1-\phi) - \lambda\gamma\beta_{h_1}\pi_{h_2}(1-\phi),\\ &\leq \gamma\lambda\pi_{h_2} - \gamma\lambda\beta_{h_2}(\phi+\hat{\tau}).\end{aligned}$$

And from equation (2.1.10) we have that

$$\frac{d\beta_{h_2}}{dt} \leq \gamma\lambda\pi_{h_2} - \gamma\lambda\beta_{h_2}(\phi+\hat{\tau}).$$

Again proceeding as in the proof of Lemma 2.4.3 we deduce that

$$\beta_{h_2}^{\infty} \leq \frac{\pi_{h_2}^{\infty}}{\phi+\hat{\tau}}.$$

For β_y for both Assumption 1 and Assumption 2 we have that

$$\begin{aligned}\frac{d\beta_y}{dt} &= \lambda\gamma\pi_y - \lambda\gamma\beta_y(\phi+\hat{\tau}) - \lambda\gamma\pi_y(\beta_{h_1}+\beta_{h_2})(1-\phi)\\ &\quad -\lambda\gamma\beta_y\pi_y(1-\phi) - \beta_y(\pi_{h_1}+\pi_{h_2})(1-\phi),\\ &\leq \lambda\gamma\pi_y - \lambda\gamma\beta_y(\phi+\hat{\tau}).\end{aligned}$$

So once again we have that

$$\beta_y^{\infty} \leq \frac{\pi_y^{\infty}}{\phi+\hat{\tau}}.$$

Now for Assumption 1 and Assumption 2, we have that

$$\beta_{h_1}^{\infty} \leq \frac{\pi_{h_1}^{\infty}}{\phi+\hat{\tau}}, \quad \beta_{h_2}^{\infty} \leq \frac{\pi_{h_2}^{\infty}}{\phi+\hat{\tau}} \text{ and } \quad \beta_y^{\infty} \leq \frac{\pi_y^{\infty}}{\phi+\hat{\tau}}. \tag{2.4.18}$$

Again if we compare this with Corson (2011) and Corson et al. (2012) then we can see this is different than both Corson (2011) and Corson et al. (2012) because of the ϕ.

The next step in our argument is to derive a relationship between $\pi_{h_1}^{\infty}$ and $\pi_{h_2}^{\infty}$ given by the following Lemma:

Lemma 2.4.4.

$$(1-\delta)\pi_{h_2}^{\infty} = \delta\pi_{h_1}^{\infty}.$$

Proof. Following a similar proof of Lemma 3.2 in Corson (2011) and Lemma 4.2 in Corson et al. (2012). □

Define $\pi_h = \pi_{h_1} + \pi_{h_2}$. Suppose that $\pi_h^\infty > 0$. Using the previous lemma it is straightforward to show that

$$\pi_h^\infty = \frac{\pi_{h_1}^\infty}{(1-\delta)} = \frac{\pi_{h_2}^\infty}{\delta}.$$

We can use Lemma 2.4.4 to write the inequalities in Lemma 2.4.3, Corollary 2.4.1 and equations (2.4.18) in terms of π_h^∞ to obtain:

$$\pi_y^\infty \leq \frac{\sigma(1-\delta)\pi_h^\infty}{\mu+\psi}, \tag{2.4.19}$$

$$\pi_z^\infty \leq \frac{\sigma\delta\alpha\pi_h^\infty}{\mu}, \tag{2.4.20}$$

$$\beta_{h_1}^\infty \leq \frac{(1-\delta)\pi_h^\infty}{\phi+\hat{\tau}}, \tag{2.4.21}$$

$$\beta_{h_2}^\infty \leq \frac{\delta\pi_h^\infty}{\phi+\hat{\tau}} \qquad \text{and} \tag{2.4.22}$$

$$\beta_y^\infty \leq \frac{\sigma(1-\delta)\pi_h^\infty}{(\mu+\psi)(\phi+\hat{\tau})}. \tag{2.4.23}$$

Adding equations (2.1.3) and (2.1.4) together we have

$$\begin{aligned}
\frac{d\pi_h}{dt} &= \lambda(1-\phi)(1-\pi_h-\pi_y-\pi_z)(\alpha_h(\beta_{h_1}+\beta_{h_2})+\alpha_y\beta_y) - (\mu+\sigma)\pi_h, \\
&\leq \lambda(1-\phi)(1-\pi_h)(\alpha_h(\beta_{h_1}^\infty+\beta_{h_2}^\infty)+\alpha_y\beta_y^\infty+\epsilon) - (\mu+\sigma)\pi_h, \\
&\qquad\qquad \text{for } \epsilon > 0,\ t \geq t_3(\epsilon) \text{ for some } t_3(\epsilon) > 0.
\end{aligned}$$

Substituting in the upper bounds for $\beta_{h_1}^\infty$, $\beta_{h_2}^\infty$ and β_y^∞ given by inequalities (2.4.21)-(2.4.23) yields

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

where $\epsilon_2 = \frac{\epsilon\lambda(1-\phi)}{(\mu+\sigma)}$. Using equation (2.3.13) we obtain

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

Following a similar proof as in Corson (2011), so for all $t \geq t_3(\epsilon)$ and by integrating over $[t_3(\epsilon), t]$ and using a similar method to that used in the proof of Lemma 2.4.3 we have that

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

such that ϵ_4 is an arbitrarily small positive constant. Since if $0 \leq R_0 \leq 1$ then we deduce that

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

Because $\epsilon_5 > 0$ is arbitrarily then we can write

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

As in Corson (2011) and Corson et al. (2012) this results in a contradiction and hence we deduced that $\pi_h^\infty = 0$ provided that $0 \leq R_0 \leq 1$. So as a result $\pi_{h_1}^\infty = \pi_{h_2}^\infty = \pi_y^\infty = \pi_z^\infty = \beta_{h_1}^\infty = \beta_{h_2}^\infty = \beta_y^\infty = 0$. Therefore the DFE is globally stable when $0 \leq R_0 \leq 1$ (see Theorem 3.2, Corson 2011).

Thus we have shown that if $R_0 \leq 1$ the DFE is globally asymptotically stable. We next turn our attention to the situation where $R_0 > 1$, recall that in this case there is a unique endemic equilibrium. Our first result is the following lemma which shows that if $R_0 > 1$ then the DFE is unstable.

Theorem 2.4.5. *If $R_0 > 1$ the DFE is unstable.*

Proof. If we are using the similar method which was used in proving of Theorem 3.3 in Corson (2011) and proving of Theorem 4.3 in Corson et al. (2012) and considering the linearised system of equations (2.1.1)-(2.1.11) which are evaluated at the DFE. Also, when linearising the population dynamics in the neighbourhood of the disease-free equilibrium point then we have that $d\boldsymbol{x}/dt = \boldsymbol{J}\boldsymbol{x}$, where $\boldsymbol{x}^T = (1-\pi_{\boldsymbol{x}}, \pi_{\boldsymbol{x}_1}, \pi_{\boldsymbol{h}_1}, \pi_{\boldsymbol{h}_2}, \pi_{\boldsymbol{y}}, \pi_{\boldsymbol{z}}, \beta_{\boldsymbol{h}_1}, \beta_{\boldsymbol{h}_2}, \beta_{\boldsymbol{y}})$ then this leads us to have one $\boldsymbol{J}$ matrix for both Assumption 1 and Assumption 2 which is given by

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

Using the Routh-Hurwitz conditions then we need just to show that for instability the constant term $a_9 < 0$, in the characteristic equation of $\boldsymbol{J}$. Now the characteristic equation of the matrix $\boldsymbol{J}$ is a ninth-order polynomial in ω, which is in the form:

$$\omega^9 + a_1\omega^8 + a_2\omega^7 + a_3\omega^6 + a_4\omega^5 + a_5\omega^4 + a_6\omega^3 + a_7\omega^2 + a_8\omega + a_9 = 0.$$

It is straightforward to show that

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

As in Corson (2011) and Corson et al. (2012), this term is negative when $R_0 > 1$ and the result follows. □

Our main persistence result is Theorem 2.4.10 which states that if $R_0 > 1$ then these terms cannot become arbitrarily small, hence can be bounded away from the origin.

This shows that if infection is initially present in either PWIDs or needles and $R_0 > 1$ then infection will persist indefinitely. As with Theorem 2.4.2, we are going

to prove this in several stages. Hence, we need some preliminary lemmas. Let

$$\pi_{h_1,\infty} = \liminf_{t\to\infty} \pi_{h_1}(t),$$

$$\pi_{h_2,\infty} = \liminf_{t\to\infty} \pi_{h_2}(t),$$

$$\pi_{y,\infty} = \liminf_{t\to\infty} \pi_{y}(t),$$

$$\pi_{z,\infty} = \liminf_{t\to\infty} \pi_{z}(t),$$

$$\beta_{h_1,\infty} = \liminf_{t\to\infty} \beta_{h_1}(t),$$

$$\beta_{h_2,\infty} = \liminf_{t\to\infty} \beta_{h_2}(t),$$

$$\beta_{y,\infty} = \liminf_{t\to\infty} \beta_{y}(t).$$

Lemma 2.4.6. *If* $\pi_{y,\infty} = \lim_{t\to\infty} \inf \pi_y(t)$*, then*

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

Proof. From equation (2.1.5) we have, given $\epsilon > 0$ then

$$\begin{aligned}\frac{d}{dt}[\pi_y \exp((\mu+\psi)t)] &= \sigma\pi_{h_1} \exp((\mu+\psi)t),\\ &\geq \sigma(\pi_{h_1,\infty} - \epsilon)\exp((\mu+\psi)t), \quad \forall\ t \geq t_4(\epsilon), \text{ for some} \quad t_4(\epsilon) > 0.\end{aligned}$$

Now integrating over $[t_4(\epsilon), t]$ gives

$$\begin{aligned}\pi_y(t)\exp((\mu+\psi)t) \geq \pi_y(t_4(\epsilon))\exp((\mu+\psi)t_4(\epsilon)) + (\pi_{h_1,\infty}-\epsilon)\sigma\frac{1}{\mu+\psi}(\exp(\mu+\psi)t\\ - \exp(\mu+\psi)t_4(\epsilon)).\end{aligned}$$

Dividing by $\exp((\mu+\psi)t)$,

$$\pi_y(t) \geq \pi_y(t_4(\epsilon))\exp[-(\mu+\psi)(t-t_4(\epsilon))] + (\pi_{h_1,\infty}-\epsilon)\frac{\sigma}{\mu+\psi}[1-\exp(-(\mu+\psi)(t-t_4(\epsilon)))].$$

Now note that $\exp(-(\mu+\psi)(t-t_4(\epsilon))) \to 0 \quad \text{as} \quad t\to\infty$. So there exists $t_5(\epsilon) > t_4(\epsilon)$ such that for $t \geq t_5(\epsilon)$,

$$\pi_y(t) \geq \frac{\sigma\pi_{h_1,\infty}}{\mu+\psi} - \epsilon_6, \qquad \text{where} \quad \epsilon_6 = \epsilon\frac{\mu+\psi+\sigma}{\mu+\psi}.$$

As ϵ is arbitrary the result of Lemma 2.4.6 follows. □

Lemma 2.4.7.

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

Proof. Using equation (2.1.6) and the same method used in the previous lemma then the result follows.

In order to prove Theorem 2.4.2 we needed to find a relationship between $\pi_{h_1}^{\infty}$ and $\pi_{h_2}^{\infty}$. In a similar way, to prove Theorem 2.4.10 we need to find a relationship between $\pi_{h_1,\infty}$ and $\pi_{h_2,\infty}$.

Lemma 2.4.8.

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

Proof. Following a similar proof of Lemma 3.5 in Corson (2011) and Lemma 4.3 in Corson et al. (2012).

Using the same method as Lemma 2.4.6 and equations (2.1.7), (2.1.9), (2.4.14) and (2.4.15) for both Assumption 1 and Assumption 2 it is straightforward to show that

$$\beta_{h_1,\infty} \geq \frac{\pi_{h_1,\infty}}{1+\hat{\tau}},\ \beta_{h,\infty} \geq \frac{\pi_{h_1,\infty}}{(1-\delta)(1+\hat{\tau})} \text{ and } \beta_{\infty} \geq \frac{\pi_{h_1,\infty}}{(1-\delta)(1+\hat{\tau})}\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}\right). \tag{2.4.24}$$

So this argument is different than Corson (2011) and Corson et al. (2012) because we have to combine the β's.

From Lemmas 2.4.6-2.4.8 and inequalities (2.4.24) we deduce that it is sufficient to show that $\pi_{h_1,\infty} > 0$ in order to bound trajectories away from zero.

Lemma 2.4.9. *Assume 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* $\pi_{h_1}(\Delta t)$, $\pi_{h_2}(\Delta t)$, $\pi_y(\Delta t)$, $\beta_{h_1}(\Delta t)$, $\beta_{h_2}(\Delta t)$, *and* $\beta_y(\Delta t)$ *are all bigger than zero for small* $\Delta t > 0$.

Proof. Similar to the proof of Lemma 3.6 in Corson (2011) and the proof of the Lemma 4.4 in Corson et al. (2012) although there are small differences in the introduction of a ψ term and the fact that the β equations are different and there are two Assumptions. □

Theorem 2.4.10. *If $R_0 > 1$ and either $\pi(0) > 0$ or $\beta(0) > 0$ is strictly positive then there exists $\epsilon > 0$ and $\eta > 0$ such that for $t > \eta$, $\pi_{h_1} \geq \epsilon\pi^*_{h_1}$, $\pi_{h_2} \geq \epsilon\pi^*_{h_2}$, $\pi_y \geq \epsilon\pi^*_y$, $\pi_z \geq \epsilon\pi^*_z$, $\beta_{h_1} \geq \epsilon\beta^*_{h_1}$, $\beta_h \geq \epsilon\beta^*_h$ and $\beta \geq \epsilon\beta^*$.*

Proof. Note that this is again different to Corson (2011) and Corson et al. (2012) because it is more complicated and we have to work with β_{h_1}, β_h and β instead of β_{h_1}, β_{h_2} and β_y. Also the bounds for the β's are different. However part of the argument is based on Corson (2011) and Corson et al. (2012).

Assume that ϵ is fixed and small. We have two cases:

1. $\pi_{h_1,\infty} \geq \frac{1}{2}\epsilon\pi^*_{h_1}$ or
2. $\pi_{h_1,\infty} < \frac{1}{2}\epsilon\pi^*_{h_1}$.

Starting first by case 1, $\pi_{h_1,\infty} \geq \frac{1}{2}\epsilon\pi^*_{h_1}$, then we have from the definition of $\pi_{h_1,\infty}$ that 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 2.4.8 we find that

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

Arguing similarly to the above there exists T_2 such that for $t \geq T_2$ then $\pi_{h_2} \geq \frac{1}{4}\epsilon\pi^*_{h_2}$.

Recall that under Assumption 1

$$\beta^*_{h_1} = \frac{\pi^*_{h_1}}{\pi^*_{h_1} + \phi(1-\pi^*_{h_1}) + \hat{\tau}},$$

and under Assumption 2

$$\beta^*_{h_1} = \frac{\pi^*_{h_1}}{\pi^*_h + \phi(1-\pi^*_h) + \hat{\tau}},$$

and also under both assumptions

$$\beta^*_h = \frac{\pi^*_h}{\pi^*_h + \phi(1-\pi^*_h) + \hat{\tau}},$$

and

$$\beta^* = \frac{\pi^*}{\pi^* + \phi(1-\pi^*) + \hat{\tau}}.$$

Hence using Lemma 2.4.6 and 2.4.7 and inequalities (2.4.24) and arguing similarly to the above we find that there exists a T_3 such that for all $t \geq T_3$, $\pi_y \geq \frac{1}{4}\epsilon\pi_y^*$, $\pi_z \geq \frac{1}{4}\epsilon\pi_z^*$, $\beta_{h_1} \geq \frac{1}{4}\epsilon\frac{\pi_{h_1}^*(1-\phi)+\phi+\hat{\tau}}{1+\hat{\tau}}\beta_{h_1}^*$ (under Assumption 1) or $\beta_{h_1} \geq \frac{1}{4}\epsilon\frac{\pi_h^*(1-\phi)+\phi+\hat{\tau}}{1+\hat{\tau}}\beta_{h_1}^*$ (under Assumption 2), $\beta_h \geq \frac{1}{4}\epsilon\frac{\pi_h^*(1-\phi)+\phi+\hat{\tau}}{1+\hat{\tau}}\beta_h^*$ and $\beta \geq \frac{1}{4}\epsilon\frac{\pi^*(1-\phi)+\phi+\hat{\tau}}{1+\hat{\tau}}\beta^*$. The inequalities apart from that for β_{h_1} are true for either assumption. So defining $\epsilon' = \frac{1}{4}\epsilon\frac{\phi+\hat{\tau}}{1+\hat{\tau}}$ we see that Theorem 2.4.10 is true with ϵ' replaced by ϵ.

Now we are dealing with case 2 where $\pi_{h_1,\infty} < \frac{1}{2}\epsilon\pi_{h_1}^*$, if we assume that $\pi_{h_1,\infty} < \frac{1}{2}\epsilon\pi_{h_1}^*$ then from Lemma 2.4.9 we can find time $r \geq \Delta t$ where $\pi_{h_1}(r) < \frac{1}{2}\epsilon\pi_{h_1}^*$. So if we define the time t_0 by $t_0 = \inf\{r \geq \triangle t, \pi_{h_1}(r) < \frac{1}{2}\epsilon\pi_{h_1}^*\}$ to be the first time which is located immediately after $t = \Delta t$ where π_{h_1} starts to go below $\frac{1}{2}\epsilon\pi_{h_1}^*$ and $t_1 = \inf\{r \geq t_0, \pi_{h_1}(r) > \frac{1}{2}\epsilon\pi_{h_1}^*\}$ to be the first time which is also located immediately after $t = t_0$ where π_{h_1} increases over $\frac{1}{2}\epsilon\pi_{h_1}^*$. If $\pi_{h_1}(\Delta t) \geq \frac{1}{2}\epsilon\pi_{h_1}^*$ then by the definition of t_0, we have $\pi_{h_1}(t_0+\omega) < \frac{1}{2}\epsilon\pi_{h_1}^*$ for some ω 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 are going now to show that if π_{h_1} becomes small then all other variables must also become also small. □

Lemma 2.4.11. *There exists a time $T_1^* > 0$ such that if $t_0 + T_1^* < t_1$ then for all $t \in [t_0+T_1^*, t_1], 0 < \pi_y < (\frac{1}{2}+\Delta)\epsilon\pi_y^*$ where T_1^* depends only on the model parameters, Δ and ϵ.*

Proof. We have that $\pi_{h_1} \leq \frac{1}{2}\epsilon\pi_{h_1}^*$ in $[t_0, t_1]$. Using equation (2.1.5) then we have

$$\frac{d}{dt}(\pi_y \exp((\mu+\psi)t)) \leq \frac{1}{2}\epsilon\pi_{h_1}^*\sigma\exp((\mu+\psi)t).$$

Integrating over $[t_0, t]$,

$$[\pi_y \exp((\mu+\psi)t)]_{t_0}^t \leq \frac{1}{2}\epsilon\pi_{h_1}^*\sigma\left(\frac{e^{(\mu+\psi)t} - e^{(\mu+\psi)t_0}}{\mu+\psi}\right),$$

we deduce that

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

Provided that t is sufficiently large, let $t \geq t_0 + T_1^*$ then the result holds. □

In Lemma 2.4.11 we have seen that π_{h_1} becomes small then this leads π_y to become small. We shall now prove similar results for π_{h_2}, π_z, β_{h_1}, β_h and β.

Lemma 2.4.12. *There exists a time $T_2^* > 0$ such that for $t \in (t_0 + T_2^*, t_1)$ then $0 < \pi_{h_2} < \left(\frac{1}{2} + \Delta\right)\epsilon\pi_{h_2}^*$, where T_2^* depends only on the model parameters, $\triangle$ and ϵ.*

Proof. From the proof of Lemma 2.4.4 we have

$$\left|\frac{\pi_{h_1}}{1-\delta} - \frac{\pi_{h_2}}{\delta}\right| \leq \left|\frac{\pi_{h_1}(0)}{1-\delta} - \frac{\pi_{h_2}(0)}{\delta}\right| e^{-(\mu+\sigma)t},$$

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

Using the triangle inequality, we have that

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

Hence in the interval $[t_0, t_1]$,

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

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

Lemma 2.4.13. *There exists a time $T_3^* > 0$ such that for $t \in (t_0 + T_2^* + T_3^*, t_1), 0 < \pi_z < (\frac{1}{2} + 2\Delta)\epsilon\pi_z^*$, where T_3^* depends only on the model parameters, Δ and ϵ.*

Proof. Using equation (2.1.6) and Lemma 2.4.12 then we have in $(t_0 + T_2^*, t_1)$,

$$\frac{d}{dt}(\pi_z \exp(\mu t)) \leq \left(\frac{1}{2} + \Delta\right)\sigma\alpha\pi_{h_2}^* \exp(\mu t).$$

Integrating over $[t_0 + T_2^*, t]$ then

$$\pi_z(t) \leq e^{-\mu(t-t_0-T_2^*)} + \left(\frac{1}{2} + \Delta\right)\epsilon\pi_z^*.$$

Thus, provided that t is large enough, the lemma is true. □

Lemma 2.4.14. *There exists a time $T_4^* > 0$ such that for $t \in (t_0 + T_4^*, t_1)$, where T_4^* depends only on the model parameters Δ and ϵ then*

$$0 < \beta_{h_1} < \left(\frac{1}{2} + \Delta\right)\epsilon_1\beta_{h_1}^*,$$

where

$$\epsilon_1 = \epsilon \, \frac{(\pi^*_{h_1}(1-\phi) + \hat{\tau} + \phi)}{\hat{\tau} + \phi} > \epsilon,$$

for Assumption 1 and

$$\epsilon_1 = \epsilon \, \frac{(\pi^*_{h}(1-\phi) + \hat{\tau} + \phi)}{\hat{\tau} + \phi} > \epsilon,$$

for Assumption 2.

Proof. We have that for both Assumption 1 and Assumption 2

$$\frac{d\beta_{h_1}}{dt} \leq \lambda\gamma\pi_{h_1} - \lambda\gamma\beta_{h_1}(\phi + \hat{\tau}).$$

Hence,

$$\begin{aligned}\frac{d}{dt}\big[\beta_{h_1}\exp[(\lambda\gamma\phi+\tau)t]\big] &\leq \lambda\gamma\pi_{h_1}\exp\big[(\lambda\gamma\phi+\tau)t\big], \\ &\leq \frac{1}{2}\epsilon\lambda\gamma\pi^*_{h_1}\exp\big[(\lambda\gamma\phi+\tau)t\big] \qquad \text{in } [t_0,t].\end{aligned}$$

Arguing as in the proof of Lemma 2.4.11

$$\beta_{h_1}(t) \leq \frac{(\frac{1}{2}+\Delta)}{\hat{\tau}+\phi}\pi^*_{h_1}\epsilon,$$

for t sufficiently large, say $t \geq t_0 + T^*_4$. However we cannot replace $\frac{\pi^*_{h_1}}{\hat{\tau}+\phi}$ by $\beta^*_{h_1}$ since under Assumption 1

$$\beta^*_{h_1} = \frac{\pi^*_{h_1}}{\pi^*_{h_1}(1-\phi)+\hat{\tau}+\phi} \leq \frac{\pi^*_{h_1}}{\hat{\tau}+\phi},$$

and under Assumption 2

$$\beta^*_{h_1} = \frac{\pi^*_{h_1}}{(\pi^*_{h_1}+\pi^*_{h_2})(1-\phi)+\hat{\tau}+\phi} \leq \frac{\pi^*_{h_1}}{\hat{\tau}+\phi}.$$

So defining ϵ_1 as in Lemma 2.4.14 we have the required result. □

Lemma 2.4.15. *There exists a time $T^*_5 > 0$ such that for $t \in (t_0 + T^*_2 + T^*_5, t_1)$, where T^*_5 depends only on the model parameters Δ and ϵ then*

$$0 < \beta_h < \left(\frac{1}{2} + 2\Delta\right)\epsilon_2\beta^*_h,$$

for both Assumption 1 and Assumption 2 where

$$\epsilon_2 = \left(\frac{\pi^*_h(1-\phi)+\hat{\tau}+\phi}{\hat{\tau}+\phi}\right)\epsilon > \epsilon.$$

Proof. Note that for both Assumption 1 and Assumption 2 we have

$$\frac{d\beta_h}{dt} \leq \lambda\gamma\pi_h - \lambda\gamma(\phi+\hat{\tau})\beta_h.$$

So arguing as in the proof of Lemma 2.4.14 we can deduce that there exists $T_5^* > 0$ depending only on the model parameters Δ and ϵ such that for $t \in [t_0 + T_2^* + T_5^*, t_1]$

$$\beta_h \leq \left(\frac{1}{2} + 2\Delta\right)\frac{\pi_h^*}{\phi+\hat{\tau}}\epsilon.$$

Now noting that

$$\beta_h^* = \frac{\pi_h^*}{\pi_h^*(1-\phi)+\phi+\hat{\tau}},$$

the result follows. □

Lemma 2.4.16. *There exists a time $T_6^* > 0$ such that for $t \in (t_0+T_1^*+T_2^*+T_6^*, t_1)$, where T_6^* depends only on the model parameters Δ and ϵ then*

$$0 < \beta < \left(\frac{1}{2} + 3\Delta\right)\epsilon_2\beta^*,$$

for both Assumption 1 and Assumption 2 where

$$\epsilon_3 = \left(\frac{\pi^*(1-\phi)+\hat{\tau}+\phi}{\hat{\tau}+\phi}\right)\epsilon > \epsilon.$$

Proof. Similar to the proof of Lemma 2.4.15 as

$$\frac{d\beta}{dt} \leq \lambda\gamma\pi - \lambda\gamma(\phi+\hat{\tau})\beta.$$

□

We have shown that if π_{h_1} approaches zero then all components must also approach zero. Now we show that π_{h_1} cannot become arbitrary small. We do this by showing that $t_1 - t_0$ can be bounded above by a fixed finite value and hence, π_{h_1} cannot remain below $\frac{1}{2}\epsilon\pi_{h_1}^*$ long enough to become arbitrary close to zero. We have either

1. $t_1 \geq t_0 + \max[T_1^*+T_2^*+T_3^*, T_2^*+T_5^*, T_1^*+T_2^*+T_6^*]$ or
2. $t_1 < t_0 + \max[T_1^*+T_2^*+T_3^*, T_2^*+T_5^*, T_1^*+T_2^*+T_6^*]$.

Again the basic idea of the proof is similar to Corson (2011) and Corson et al. (2012). Therefore, if case (2) is true, then our proof is complete. We want to show case (1) where t_1 occurs at a time higher than or equal to the time it takes for all terms to become small. So if we are using the instability of the DFE where $R_0 > 1$ we will see that π_{h_1} cannot stay small indefinitely.

Lemma 2.4.17. *Let $F_1(\omega, \epsilon)$ be an nth degree polynomial in ω and ϵ. Denote the (possibly complex) roots of $F_1(\omega, \epsilon) = 0$ by ω_j for $j = 1, ..., n$. Then each ω_j is defined and continuous in ϵ in a neighbourhood of $\epsilon = 0$.*

Proof. See Lewis (2000). □

Lemma 2.4.18. *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 $t = t_0 + \max[T^*_1 + T^*_2 + T^*_3, T^*_1 + T^*_5, T^*_1 + T^*_2 + T^*_6, t_0 + t_2 + T^*_7]$ which is finite and depends only on the model parameters, Δ and ϵ.*

Proof. Although there are similarities with the proof of Corson (2011) and Corson et al. (2012) there are significant differences. In particular a different co-ordinate system is used. Consider the model with re-arranged co-ordinate system $\tilde{\boldsymbol{x}}^T = (\pi_x, \pi_{x_1}, \pi_z, \ \beta_{h_1}, \pi_{h_1}, \pi_{h_2}, \pi_y, \beta_h, \beta)$ linearised about the disease-free equilibrium. We see clearly that the three of the eigenvalues are $-\mu$ and one is $-(\lambda\gamma\phi + \tau)$ (for both assumptions).

For $\epsilon \geq 0$ define the matrix $\boldsymbol{J}_1(\epsilon) =$

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

The linearised stability matrix is

$$\boldsymbol{J}(0) = \begin{bmatrix} -\boldsymbol{D} & \boldsymbol{X} \\ \boldsymbol{0} & \boldsymbol{J}_1(0) \end{bmatrix}.$$

Here $\boldsymbol{D}$ is the matrix

$$\begin{bmatrix} -\mu & 0 & 0 & 0 \\ 0 & -\mu & 0 & 0 \\ 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & -(\phi\lambda\gamma + \tau) \end{bmatrix}.$$

Define the matrix

$$\boldsymbol{J}(\epsilon) = \begin{bmatrix} -\boldsymbol{D} & \boldsymbol{X} \\ \boldsymbol{0} & \boldsymbol{J}_1(\epsilon) \end{bmatrix}.$$

Denote the eigenvalues of $\boldsymbol{J}(\epsilon)$ by $\omega_i(\epsilon)$, $i = 1, 2, 3, ..., 9$. Five of the eigenvalues, $\omega_i(\epsilon)$, $i = 1, 2, 3, 4, 5$ come from $\boldsymbol{J}_1(\epsilon)$, with the other four eigenvalues equal to $-\mu$, $-\mu$, $-\mu$ and $-(\phi\lambda\gamma + \tau)$. Arguing as in the proof of Lemma 3.10 in Corson (2011) and the proof of Lemma 4.8 in Corson et al. (2012) by taking ϵ_7 sufficiently small we can ensure that $\omega_1(\epsilon_7) > 0$. With this choice of ϵ_7 we can choose ϵ small enough so that

$$\frac{1}{2}\epsilon\pi^*_{h_1} + \left(\frac{1}{2} + \triangle\right)\epsilon\pi^*_{h_2} + \left(\frac{1}{2} + \triangle\right)\epsilon\pi^*_y + \left(\frac{1}{2} + 2\triangle\right)\epsilon\pi^*_z < \epsilon_7.$$

Hence for $t_1 > t > t_0 + T^*_1 + T^*_2 + T^*_3$ we have $\pi^+(t) = \pi + \pi_z < \epsilon_7$.

Therefore we have for both Assumption 1 and Assumption 2

$$\begin{aligned}
\frac{d\pi_{h_1}}{dt} &\geq (1-\epsilon_7)(1-\delta)\lambda(1-\phi)((\alpha_h - \alpha_y)\beta_h + \alpha_y\beta) - (\mu+\sigma)\pi_{h_1}, \\
\frac{d\pi_{h_2}}{dt} &\geq (1-\epsilon_7)\lambda\delta(1-\phi)((\alpha_h - \alpha_y)\beta_h + \alpha_y\beta) - (\mu+\sigma)\pi_{h_2}, \\
\frac{d\pi_y}{dt} &\geq \sigma\pi_{h_1} - (\mu+\psi)\pi_y, \\
\frac{d\beta_h}{dt} &\geq \lambda\gamma\pi_h - \beta_h(\lambda\gamma(1-\phi)\epsilon_7 + \lambda\gamma\phi + \tau), \\
\frac{d\beta}{dt} &\geq \lambda\gamma\pi - \beta(\lambda\gamma(1-\phi)\epsilon_7 + \lambda\gamma\phi + \tau).
\end{aligned}$$

In matrix form we now have $\frac{d\boldsymbol{x}_1}{dt} \geq \boldsymbol{J}_1(\epsilon_7)\boldsymbol{x}_1$ where $\boldsymbol{x}_1 = (\pi_{h_1}, \pi_{h_2}, \pi_y, \beta_h, \beta)$. Let $t_2 = \inf\{\xi \geq 0 : \text{ for } t_1 > t > t_0 + \xi, \quad \pi(t) < \epsilon_7\}$. So if $t_2 > 0$ then by continuity $\pi(t_0 + t_2) = \epsilon_7$ and so $t_0 + t_2$ is the last time before t_1 that $\pi(t) \geq \epsilon_7$. Note that $t_2 \leq T_1^* + T_2^* + T_3^*$. If $t_1 < t_0 + T_1^* + T_2^* + T_3^*$ we have the desired result. Consider the case where $t_1 \geq t_0 + T_1^* + T_2^* + T_3^*$, we have that $\frac{d\boldsymbol{x}_1}{dt} \geq \boldsymbol{J}_1(\epsilon_7)\boldsymbol{x}_1$ for $(t_0 + t_2, t_1]$, also $\boldsymbol{J}_1(\epsilon_7)$ has a strictly positive left eigenvector $\boldsymbol{e} = (e_1, e_2, e_3, e_4, e_5)$, which corresponds to its spectral radius $\omega_1(\epsilon_7)$. Hence

$$\boldsymbol{e} \cdot \frac{d\boldsymbol{x}_1}{dt} \geq \boldsymbol{e} \cdot \boldsymbol{J}_1(\epsilon_7)\boldsymbol{x}_1 = \omega(\epsilon_7)\boldsymbol{e} \cdot \boldsymbol{x}_1.$$

Thus for $t > t_0 + t_2$,

$$\begin{aligned}
\boldsymbol{e} \cdot \boldsymbol{x}_1(t) &\geq (\boldsymbol{e} \cdot \boldsymbol{x}_1)(t_0 + t_2) \exp[\omega_1(\epsilon_7(t - t_0 - t_2))], \text{ integrating over } [t_0 + t_2, t], \\
&\geq \pi(t_0 + t_2) \min(e_1, e_2, e_3) \exp[\omega_1(\epsilon_7(t - t_0 - t_2))], \\
&= \epsilon_7 \min(e_1, e_2, e_3) \exp[\omega_1(\epsilon_7(t - t_0 - t_2))], \text{ if } t_2 > 0, \\
&\geq \frac{1}{2}\epsilon\pi_{h_1}^* \min(e_1, e_2, e_3) \exp[\omega_1(\epsilon_7)(t - t_0)] \text{ if } t_2 = 0, \text{ and } \pi_{h_1}(\triangle t) \geq \frac{1}{2}\epsilon\pi_{h_1}^*,
\end{aligned}$$

so that $\pi_{h_1}(t_0) = \frac{1}{2}\epsilon\pi_{h_1}^*$.

Therefore, if either $t_2 > 0$ or $\pi_{h_1}(\triangle t) \geq \frac{1}{2}\epsilon\pi_{h_1}^*$, after a time $t_0 + t_2 + T_7^*$, we have

$$\boldsymbol{e}\cdot\boldsymbol{x}_1(t) > \boldsymbol{e}\cdot\left(\frac{1}{2}\epsilon\pi_{h_1}^*, \left(\frac{1}{2}+\triangle\right)\epsilon\pi_{h_2}^*, \left(\frac{1}{2}+\triangle\right)\epsilon\pi_y^*, \left(\frac{1}{2}+2\triangle\right)\epsilon_2\beta_h^*, \left(\frac{1}{2}+3\triangle\right)\epsilon_3\beta^*\right). \tag{2.4.25}$$

Here T_7^* depends only on $\epsilon, \triangle$ and the model parameters. If $t_1 \geq t_0 + \max[T_1^* + T_2^* + T_3^*, T_2^* + T_5^*, T_1^* + T_2^* + T_6^*, t_2 + T_7^*]$ then for $t \geq t_0 + \max[T_1^* + T_2^* + T_3^*, T_2^* + T_5^*, T_1^* + T_2^* + T_6^*, t_2 + T_7^*]$ we have $\pi_{h_1} \leq \frac{1}{2}\epsilon\pi_{h_1}^*$, $\pi_{h_2} \leq \left(\frac{1}{2}+\Delta\right)\epsilon\pi_{h_2}^*$, $\pi_y \leq \left(\frac{1}{2}+\Delta\right)\epsilon\pi_y^*$, $\beta_{h_1+h_2} \leq \left(\frac{1}{2} + 2\triangle\right)\epsilon_2\beta_h^*$, $\beta \leq \left(\frac{1}{2} + 3\triangle\right)\epsilon_3\beta^*$. Hence

$$\boldsymbol{e}\cdot\boldsymbol{x}_1(t) < \boldsymbol{e}\cdot\left(\frac{1}{2}\epsilon\pi_{h_1}^*, \left(\frac{1}{2}+\triangle\right)\epsilon\pi_{h_2}^*, \left(\frac{1}{2}+\triangle\right)\epsilon\pi_y^*, \left(\frac{1}{2}+2\triangle\right)\epsilon_2\beta_h^*, \left(\frac{1}{2}+3\triangle\right)\epsilon_3\beta^*\right).$$

This is a contradiction to (2.4.25) and hence $t_1 < t_0 + \max[T_1^* + T_2^* + T_3^*, T_2^* + T_5^*, T_1^* + T_2^* + T_6^*, t_2 + T_7^*]$. Again the argument is modified from Corson (2011) and Corson et al. (2012) because there are only two β terms and the basis is different.This completes the proof of Lemma 2.4.18. □

We have shown that the first time π_{h_1} drops below $\frac{1}{2}\epsilon\pi^*_{h_1}$, it must return to this level after a duration of at most $T = \max[T^*_1+T^*_2+T^*_3, T^*_2+T^*_5, T^*_1+T^*_2+T^*_6, t_2+T^*_7]$. The main persistence result follows as in Corson (2011) and Corson et al. (2012). This completes the proof of our main persistence result Theorem 2.4.10.

2.4.3 Local stability of the endemic equilibrium

To show local stability of our model then we need to use the quasi-steady-state approximation (QSSA) and the Routh-Hurwitz conditions and this because the characteristic equation of our model equations is a ninth order polynomial then this would be impractical due to level of complexity and difficulty. In its place, a similar approximation model will be used that has five dimensions. The first concept in reducing the complexity of the system is that individual PWID demographic processes are much slower than the timescale on which individual PWIDs inject and the former are measured in years whilst the latter are measured in days. As a similar technique which was used in Corson (2011) and Corson et al. (2012) we replace β_h and β by their equilibrium values if π and π_h are constant

$$\beta_h = \frac{\pi_h}{\pi_h + (1-\pi_h)\phi + \hat{\tau}},$$

and

$$\beta = \frac{\pi}{\pi + (1-\pi)\phi + \hat{\tau}}.$$

As in Corson (2011) and Corson et al. (2012) we can eliminate 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. Therefore our approximate model can be represented by the following system of differential equations:

$$\frac{d\pi_{x_1}}{dt} = \sigma(1-\alpha)\pi_{h_2} - \mu\pi_{x_1} - \lambda(1-\phi)\left(\frac{\alpha_y\pi}{\pi + (1-\pi)\phi + \hat{\tau}} + \frac{(\alpha_h - \alpha_y)\pi_h}{\pi_h + (1-\pi_h)\phi + \hat{\tau}}\right)\pi_{x_1}, \tag{2.4.26}$$

$$\frac{d\pi_{h_1}}{dt} = \lambda(1-\phi)(1-\delta)(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z) \times \left(\frac{\alpha_y\pi}{\pi+(1-\pi)\phi+\hat{\tau}} + \frac{(\alpha_h-\alpha_y)\pi_h}{\pi_h+(1-\pi_h)\phi+\hat{\tau}}\right) - (\mu+\sigma)\pi_{h_1}, \tag{2.4.27}$$

$$\frac{d\pi_{h_2}}{dt} = \lambda(1-\phi)\delta(1-\pi_{h_1}-\pi_{h_2}-\pi_y-\pi_z)\left(\frac{\alpha_y\pi}{\pi+(1-\pi)\phi+\hat{\tau}} + \frac{(\alpha_h-\alpha_y)\pi_h}{\pi_h+(1-\pi_h)\phi+\hat{\tau}}\right) - (\mu+\sigma)\pi_{h_2}, \tag{2.4.28}$$

$$\frac{d\pi_y}{dt} = \sigma\pi_{h_1} - (\mu+\psi)\pi_y, \tag{2.4.29}$$

and

$$\frac{d\pi_z}{dt} = \sigma\alpha\pi_{h_2} - \mu\pi_z. \tag{2.4.30}$$

Note that these equations have the same equilibrium solutions and R_0 as the full model. Again this is different to Corson (2011) and Corson et al. (2012) because of the ψ term and the way that the β terms approximate the π terms.

Also by using the next generation matrix approach as we have done for the original model. Therefore, for our approximate model there are three types of infectious entities h_1, h_2 and y for individual PWIDs. Again we work with the equations representing the absolute number of PWIDs. The infectious compartments are h_1, h_2 and y.

$$\frac{dh_1}{dt} = \lambda(1-\phi)(1-\delta)(n-h_1-h_2-y-z) \times \left(\frac{\alpha_y(h+y)}{(h+y)+(n-h-y)\phi+n\hat{\tau}} + \frac{(\alpha_h-\alpha_y)h}{h+(n-h)\phi+n\hat{\tau}}\right) - (\mu+\sigma)h_1,$$

$$\frac{dh_2}{dt} = \lambda(1-\phi)\delta(n-h_1-h_2-y-z) \times \left(\frac{\alpha_y(h+y)}{(h+y)+(n-h-y)\phi+n\hat{\tau}} + \frac{(\alpha_h-\alpha_y)h}{h+(n-h)\phi+n\hat{\tau}}\right) - (\mu+\sigma)h_2,$$

$$\frac{dy}{dt} = \sigma h_1 - (\mu+\psi)y.$$

Hence we derive the next generation matrix as follows:

$$F_1 = \lambda(1-\phi)(1-\delta)(n-h_1-h_2-y-z) \times \left(\frac{\alpha_y(h+y)}{(h+y)+(n-h-y)\phi+n\hat{\tau}} + \frac{(\alpha_h-\alpha_y)h}{h+(n-h)\phi+n\hat{\tau}}\right),$$

$$F_2 = \lambda(1-\phi)\delta(n-h_1-h_2-y-z) \times \left(\frac{\alpha_y(h+y)}{(h+y)+(n-h-y)\phi+n\hat{\tau}} + \frac{(\alpha_h-\alpha_y)h}{h+(n-h)\phi+n\hat{\tau}}\right),$$

$$F_3 = \sigma h_1.$$

$$V_1(x) = (\mu+\sigma)h_1,$$
$$V_2(x) = (\mu+\sigma)h_2,$$
$$V_3(x) = (\mu+\psi)y.$$

$$\boldsymbol{F} = \begin{bmatrix} \frac{\lambda(1-\phi)(1-\delta)\alpha_h}{\phi+\hat{\tau}} & \frac{\lambda(1-\phi)(1-\delta)\alpha_h}{\phi+\hat{\tau}} & \frac{\lambda(1-\phi)(1-\delta)\alpha_y}{\phi+\hat{\tau}} \\ \frac{\lambda(1-\phi)\delta\alpha_h}{\phi+\hat{\tau}} & \frac{\lambda(1-\phi)\delta\alpha_h}{\phi+\hat{\tau}} & \frac{\lambda(1-\phi)\delta\alpha_y}{\phi+\hat{\tau}} \\ \sigma & 0 & 0 \end{bmatrix},$$

$$\boldsymbol{V} = \begin{bmatrix} (\mu+\sigma) & 0 & 0 \\ 0 & (\mu+\sigma) & 0 \\ 0 & 0 & (\mu+\psi) \end{bmatrix}.$$

Hence the next generation matrix is defined as the matrix $M = M_{ij} : i = 1, 2, 3$, $j = 1, 2, 3$ where M_{ij} is defined as the expected number of secondary cases in infectious state i caused by a single newly infectious PWID in infectious state j entering a disease free population at equilibrium. So in this case the next generation matrix is

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

Now it is important to note that for equations (2.4.26)-(2.4.30) the equilibrium values and R_0 are the same as in our original model with needles included. Recall that $\phi^* = \frac{1-\phi}{\phi+\hat{\tau}}$. If we denote R^{**} to be the basic reproduction number obtained by using the Next Generation Matrix it satisfies characteristic equation $f(\omega) = 0$ where

$$f(\omega) = \omega^2 - \alpha_h\phi^*\frac{\lambda}{\mu+\sigma}\omega - \alpha_y\phi^*\frac{\lambda\sigma(1-\delta)}{(\mu+\psi)(\mu+\sigma)}$$

and a similar argument as for the original model shows that R_0 and R_0^{**} have the same threshold value. Therefore, the characteristic equation of this matrix has eigenvalues $\omega = 0$ or the roots of

$$f(\omega) = \omega^2 - \frac{\lambda(1-\phi)\alpha_h\omega}{(\mu+\sigma)(\phi+\hat{\tau})} - \frac{\lambda(1-\phi)\sigma\alpha_y(1-\delta)}{(\mu+\psi)(\mu+\sigma)(\phi+\hat{\tau})} = 0.$$

So R_0^{**} is the unique positive root of this equation (R_0^{**} denotes the basic reproduction number of the approximate model derived by the next generation matrix method).

Again R_0^{**} and R_0 have the same threshold value as

$$\begin{aligned} R_0^{**} > 1 &\implies f(\omega) < 0 \text{ in } [0, R_0^{**}), \\ &\implies f(1) < 0, \\ &\implies 1 - R_0 < 0, \\ &\implies R_0 > 1. \end{aligned}$$

And conversely

$$\begin{aligned} R_0 > 1 &\implies f(1) < 0, \\ &\implies R_0^{**} > 1 \qquad \text{because} \qquad f(\omega) \geq 0 \quad \text{for} \quad \omega \geq R_0^{**}. \end{aligned}$$

Theorem 2.4.19. *The endemic equilibrium of this approximate model is locally stable when* $R_0 > 1$.

Proof. This proof is qualitatively different than the proof in Corson (2011) and the proof in Corson et al. (2012) because of the way the different a_1's are expressed in terms of the β's. To prove local stability we examine the Jacobian of this system linearised in the endemic equilibrium. In this system there is no π_{x_1} term in the other equations. As a result in calculating the characteristic equation from the stability matrix we are able to expand by column one giving the negative eigenvalue

$$-\mu - \lambda(1-\phi)\left(\frac{\alpha_y \pi^*}{\pi^* + (1-\pi^*)\phi + \hat{\tau}} + \frac{(\alpha_h - \alpha_y)\pi_h^*}{\pi_h^* + (1-\pi_h^*)\phi + \hat{\tau}}\right).$$

We write $K = \lambda(1-\phi)$,

$$a_1 = \frac{(\alpha_h - \alpha_y)(1-\pi^{+*})(\phi+\hat{\tau})}{(\pi_h^*(1-\phi)+\phi+\hat{\tau})^2} + \frac{\alpha_y(1-\pi^{+*})(\phi+\hat{\tau})}{(\pi^*(1-\phi)+\phi+\hat{\tau})^2} - a_3, \tag{2.4.31}$$

$$a_2 = \frac{\alpha_y(1-\pi^{+*})(\phi+\hat{\tau})}{(\pi^*(1-\phi)+\phi+\hat{\tau})^2} - a_3, \tag{2.4.32}$$

and

$$a_3 = \frac{\alpha_y \pi^*}{\pi^*(1-\phi)+\phi+\hat{\tau}} + \frac{(\alpha_h - \alpha_y)\pi_h^*}{\pi_h^*(1-\phi)+\phi+\hat{\tau}}. \tag{2.4.33}$$

Similarly to Corson (2011) and Corson et al. (2012) the remaining eigenvalues are eigenvalues of the matrix

$$\begin{vmatrix} (1-\delta)Ka_1 - (\mu+\sigma) & (1-\delta)Ka_1 & (1-\delta)Ka_2 & -(1-\delta)Ka_3 \\ \delta K a_1 & \delta K a_1 - (\mu+\sigma) & \delta K a_2 & -\delta K a_3 \\ \sigma & 0 & -(\mu+\psi) & 0 \\ 0 & \sigma\alpha & 0 & -\mu \end{vmatrix}.$$

Recall from the equilibrium analysis that

$$\pi^{+*} = k\left(1 + \frac{\sigma(1-\delta)}{\mu+\psi} + \frac{\sigma\alpha\delta}{\mu}\right), \tag{2.4.34}$$

$$\pi^* = k\left(1 + \frac{\sigma(1-\delta)}{\mu+\psi}\right),$$

$$\pi_h^* = k,$$

where k satisfies the equation

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

As in Corson (2011) and in Corson et al. (2012), one eigenvalue is $\omega = -(\mu+\sigma)$ and the remaining eigenvalues satisfy the characteristic equation

$$\omega^3 + A_1\omega^2 + A_2\omega + A_3 = 0, \tag{2.4.35}$$

where

$$A_1 = 3\mu - Ka_1 + \sigma + \psi, \tag{2.4.36}$$

$$A_2 = \sigma\alpha\delta Ka_3 + 2\mu(\mu+\psi) + \mu^2 - Ka_1(2\mu+\psi) + (2\mu+\psi)\sigma - \sigma(1-\delta)Ka_2, \tag{2.4.37}$$

$$A_3 = (\mu+\psi)\sigma\alpha\delta Ka_3 + (\mu+\sigma-Ka_1)(\mu+\psi)\mu - \mu\sigma Ka_2(1-\delta). \tag{2.4.38}$$

From the equilibrium equations we find that

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

Therefore,

$$\begin{aligned} A_1 &= 3\mu+\sigma+\psi-Ka_1 \\ &= 2\mu+(\mu+\sigma)+\psi-Ka_1. \end{aligned}$$

Substituting equation (2.4.31) into A_1 we can write

$$\begin{aligned} A_1 = 2\mu + Ka_3 + \psi &+ K\left[1-k\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}+\frac{\alpha\sigma\delta}{\mu}\right)\right] \\ &\times\left[\frac{\alpha_y\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}\right)}{k\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}\right)(1-\phi)+\phi+\hat{\tau}}+\frac{(\alpha_h-\alpha_y)}{k(1-\phi)+\phi+\hat{\tau}}\right] \\ - K\left[1-k\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}+\frac{\alpha\sigma\delta}{\mu}\right)\right] &\\ \times\left[\frac{\alpha_y(\phi+\hat{\tau})}{\left(k\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}\right)(1-\phi)+\phi+\hat{\tau}\right)^2}+\frac{(\alpha_h-\alpha_y)(\phi+\hat{\tau})}{\left(k(1-\phi)+\phi+\hat{\tau}\right)^2}\right]&. \end{aligned}$$

Hence,

$$A_1 = 2\mu + Ka_3 + \psi + \psi_1, \tag{2.4.39}$$

where

$$\psi_1 = K\left[1 - k\left(1 + \frac{\sigma(1-\delta)}{\mu+\psi} + \frac{\alpha\sigma\delta}{\mu}\right)\right] \times \left[\frac{\alpha_y \frac{\sigma(1-\delta)}{\mu+\psi}}{k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat{\tau}} + \frac{\alpha_y k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)}{\Big(k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat{\tau}\Big)^2} + \frac{(\alpha_h-\alpha_y)k(1-\phi)}{\big(k(1-\phi)+\phi+\hat{\tau}\big)^2}\right] > 0.$$

Substituting (2.4.32) in (2.4.37) we can express A_2 in terms of a_3 as

$$A_2 = Ka_3[\delta\alpha\sigma + \sigma(1-\delta)] + \mu(\mu+\psi) + (2\mu+\psi)(\mu+\sigma-Ka_1) - \sigma(1-\delta)K\zeta_2,$$

where $$\zeta_2 = \frac{\alpha_y(1-\pi^{*+})(\phi+\hat{\tau})}{(\pi^*(1-\phi)+\phi+\hat{\tau})^2}.$$

Again from equilibrium equation and equation (2.4.31) we have

$$\mu+\sigma-Ka_1 = K\left[1 - k\left(1 + \frac{\sigma(1-\delta)}{\mu+\psi} + \frac{\alpha\sigma\delta}{\mu}\right)\right] \times \left[\frac{\alpha_y \frac{\sigma(1-\delta)}{\mu+\psi}}{k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat{\tau}} + \frac{\alpha_y k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)}{\Big(k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat{\tau}\Big)^2} + \frac{(\alpha_h-\alpha_y)k(1-\phi)}{\big(k(1-\phi)+\phi+\hat{\tau}\big)^2}\right] + Ka_3.$$

Expressing $\mu+\sigma-Ka_1$ in terms of K and a_3, we have

$$A_2 = \mu(\mu+\psi) + Ka_3\big((2\mu+\psi) + \delta\alpha\sigma + \sigma(1-\delta)\big) + \psi_2, \tag{2.4.40}$$

where

$$\psi_2 = K\left[1 - k\left(1 + \frac{\sigma(1-\delta)}{\mu+\psi} + \frac{\alpha\sigma\delta}{\mu}\right)\right] \times \left[\frac{\alpha_y k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)(2\mu+\psi+\sigma(1-\delta))}{\Big(k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat{\tau}\Big)^2} + \frac{\frac{\mu}{\mu+\psi}\,\alpha_y\sigma(1-\delta)}{k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat{\tau}} + \frac{(2\mu+\psi)(\alpha_h-\alpha_y)k(1-\phi)}{\big(k(1-\phi)+\phi+\hat{\tau}\big)^2}\right] > 0. \tag{2.4.41}$$

Similarly writing

$$A_3 = (\mu+\psi)\sigma\alpha\delta K a_3 + \mu(\mu+\psi)(\mu+\sigma-Ka_1) - \mu\sigma K a_2(1-\delta), \tag{2.4.42}$$

and substituting for $\mu+\sigma-Ka_1$ and a_2 in terms of K and a_3 we see that

$$A_3 = Ka_3\big[\mu(\mu+\psi)+\sigma\alpha\delta(\mu+\psi)+\sigma(1-\delta)\mu\big]+\psi_3, \tag{2.4.43}$$

where

$$\begin{aligned}\psi_3 = \mu K&\left[1-k\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}+\frac{\alpha\sigma\delta}{\mu}\right)\right]\\ &\times\left[\frac{\alpha_y\sigma(1-\delta)k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)}{\Big(k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat\tau\Big)^2}+\frac{\alpha_y k(\mu+\psi+\sigma(1-\delta))(1-\phi)}{\Big(k\big(1+\frac{\sigma(1-\delta)}{\mu+\psi}\big)(1-\phi)+\phi+\hat\tau\Big)^2}\right.\\ &\left.+\frac{(\alpha_h-\alpha_y)k(\mu+\psi)(1-\phi)}{\big(k(1-\phi)+\phi+\hat\tau\big)^2}\right]>0.\end{aligned} \tag{2.4.44}$$

To show stability of the endemic equilibrium we need to show that the Routh-Hurwitz conditions are satisfied. These are A_1, A_2, $A_3>0$ and $A_1A_2>A_3$.

From (2.4.39), (2.4.40) and (2.4.42) it is clear that A_1, A_2 and $A_3>0$. To show $A_1A_2>A_3$ note that:

$$\begin{aligned}A_1A_2 &= (2\mu+Ka_3+\psi+\psi_1)(\mu(\mu+\psi)\\ &\quad +Ka_3\big((2\mu+\psi)+\delta\alpha\sigma+\sigma(1-\delta)\big)+\psi_2)\\ &> (2\mu+Ka_3+\psi)(\mu(\mu+\psi)+Ka_3\big((2\mu+\psi)+\delta\alpha\sigma+\sigma(1-\delta)\big))\\ &\quad +(2\mu+\psi)\psi_2,\\ &> Ka_3[\mu(\mu+\psi)+\sigma\alpha\delta(\mu+\psi)+\sigma(1-\delta)\mu]+(2\mu+\psi)\psi_2.\end{aligned} \tag{2.4.45}$$

Now we shall show that $(2\mu+\psi)\psi_2>\psi_3$. Note that

$$(2\mu+\psi)(2\mu+\psi+\sigma(1-\delta))>\mu(\mu+\psi+\sigma(1-\delta)).$$

Hence if we consider $(2\mu+\psi)$ multiplied by the first term in the second pair of square brackets in (2.4.41), it exceeds μ multiplied by the second term in the second pair of square brackets in (2.4.44). Also as

$$(2\mu+\psi)\frac{\mu}{\mu+\psi}>\mu,$$

$(2\mu + \psi)$ multiplied by the second term in the second pair of square brackets in (2.4.41), exceeds μ multiplied by the first term in the second pair of square brackets in (2.4.44). Similarly as

$$(2\mu + \psi)^2 > \mu(\mu + \psi),$$

the terms multiplying $(\alpha_h - \alpha_y)$ in $(2\mu + \psi)\psi_2$ exceed those multiplying $(\alpha_h - \alpha_y)$ in ψ_3. So

$$(2\mu + \psi)\psi_2 > \psi_3. \tag{2.4.46}$$

The result that $A_1 A_2 > A_3$ follows from (2.4.45) using (2.4.43) and (2.4.46). □

2.5 Conclusion

In this chapter we develop a deterministic compartmental model for HCV transmission among PWIDs through the sharing of needles and syringes, building on the models developed by Corson (2011) also discussed in Corson et al. (2012). Using analytical techniques, we find that the model behaviour is governed by the basic reproduction number R_0, with $R_0 = 1$ being a critical threshold separating two different outcomes. It has been shown that if $R_0 \leq 1$ there is only the disease-free equilibrium whereas if $R_0 > 1$ there is the disease-free equilibrium and a unique endemic equilibrium. This model is globally stable if $R_0 \leq 1$ otherwise unstable. After that we look at an approximate model by using the fact that the timescale on which injections take place is much faster than the timescale of epidemiological change. This approximation model has the same equilibria as the full model. Also, we showed that if $R_0 > 1$ the endemic equilibrium is locally asymptotically stable for our approximate model.

Our model is qualitatively different than the model discussed in Corson (2011) and Corson et al. (2012) because of the PWID needle interactions and the ψ term. In particular the equilibrium analysis and the local stability analysis involve substantially different arguments. It is useful to understand the behaviour of HCV both with treatment and with different PWID needle interactions. Although the assumptions that the needles take on the stage of the last infectious person to use them is common it may not be correct and it is useful to consider alternative assumptions

as we have done particularly as discussed there may be supporting evidence. The R_0 is the same for the Pessimistic Model for both Assumption 1 and Assumption 2 and always greater than the R_0 in Corson's model with the same parameters. We have derived R_0 using the Next Generation Matrix Method for both the full and approximate models and also given an alternative derivation to Corson's model.

In the next chapter we will describe numerical simulations using this simple HCV transmission model.

Chapter 3

Parameters and Numerical Simulations

HCV prevalence and incidence are still high and in the past Glasgow had one of the highest HCV prevalences of injecting drug use and HCV infection among PWIDs in Europe; of an approximate 9,000 recent PWIDs in the largest city in Scotland (Glasgow) roughly 70% had been infected with HCV (Corson (2011)). Here, the aim of this chapter is to use the simulation package Wolfram Mathematica version 11.1 to come up with hepatitis C virus (HCV) prevalence estimates. These estimates will be used to generate progression of HCV levels for the Glasgow population against time, according to the model equations in Chapter 2.

Therefore, we need to obtain values for parameters such as the probability of successful needle cleaning (ϕ), needle and syringe sharing rate (λ), needle turnover rate (τ), PWID to needle ratio (γ), rate that PWIDs leave the sharing, injecting PWID population (μ), acute and chronic HCV transmission probabilities (α_h, α_y), duration of acute HCV infection ($1/\sigma$), proportion of PWIDs that develop immunity to HCV re-infection (α), proportion of PWIDs that spontaneously resolve HCV infection (δ) and rate of treatment (ψ). The parameter values that are used are taken from the model of the model of Corson (2011) and Corson et al. (2012) except the rate of treatment (ψ) which is found from a literature review. We will make comparison between our simulation results and the results of Corson (2011).

3.1 Corson's model and our model

As we have mentioned in the previous chapter, our model is based on the 'pessimistic assumption' of Lewis and Greenhalgh (2001) and Corson's model is based on the 'optimistic assumption' of Greenhalgh and Lewis (2000). Moreover we have introduced the rate of treatment ψ in our model which was not introduced in Corson's model. Therefore there are two differences between our model and Corson's model:

1. The PWID - needle interactions have changed.
2. A treatment term has been introduced.

If we ignore the effect of treatment we expect that disease will spread faster in our model so more control effort will be needed. Moreover, we have updated the references to include recent work and included treatment of infected PWIDs in the model.

3.2 Parameters used

We take our parameters from existing published and unpublished works such as Traeger et al., Harris et al. (2019), Fraser et al. (2018), Noroozi et al. (2017), WHO (2017), Martin et al. (2011), Corson (2011), Corson et al. (2012), Goldberg et al. (1995), Kaplan and O'Keefe (1993), Greenhalgh and Lewis (2000, 2002), Murray et al. (2003), Greenhalgh and Hay (1997), Hutchinson et al. (2006a), Vickerman et al. (2009) and Vickerman et al. (2007).

Estimating the fraction of PWIDs who use of bleach to clean needles is difficult because of the very varied data available. According to Noroozi et al. (2017) the probability value of ϕ for the HCV model by 0.31 in Kermanshah, Iran. Goldberg et al. (1995) estimated the value of ϕ for the HIV model by 0.442, whereas Kaplan and O'Keefe (1993) estimate it to be 0.84. In addition, Greenhalgh and Lewis (2000, 2002) arrived at their estimate for ϕ to be 0.64 by averaging the estimates of Goldberg et al., and Kaplan and O'Keefe. Murray et al. (2003) estimate ϕ to be 0.5 modelling HCV and HIV research amongst PWIDs. The data estimated here of

$\phi = 0.255$ is from unpublished data HPS observed (1990-1993) also this value was used by Corson (2011) and Corson et al. (2012).

The data from Goldberg et al. (1995) were later used by Greenhalgh and Hay (1997), who gave an average number of shared injections $\lambda = 171$ per year after restricting the data from Goldberg et al. (1995) to those PWIDs that share. It is suggested by Goldberg et al. (1995) that the mean sharing injection rate for Glasgow PWIDs is 72.48 annually. The data estimated here of $\lambda = 103$ each year is from unpublished data HPS observed (1990-1993) also Corson (2011) and Corson et al. (2012) used the same value.

The natural lifetime of a needle estimated by Kaplan (1995) is 23.50 days which results in a natural needle turnover rate of $\tau = 365/23.5 = 15.53$ each year. Also, Greenhalgh and Lewis (2000, 2002) used this estimate when they were modelling HIV. The data from Corson (2011) and Corson et al. (2012) is used here of $\tau = 133$ every year. This is based on a survey in 2007 of 362 recent PWIDs in Greater Glasgow and Clyde.

Using information from the New Haven needle program gathered between November 1990 to February 1991,Kaplan and O'Keefe (1993) estimate that $\gamma = 0.1675$. Kaplan (1995) shows from an infectious needle model that the rate at which uncontaminated needles become contaminated with HIV is 0.3675 every day, and the rate at which contaminated needles will become uncontaminated is 0.1665 every day. Further, estimation by Corson (2011) and Corson et al. (2012) can be used here where the PWID to needle proportion γ is 1.002.

In their work on HIV in PWIDs, Greenhalgh and Hay (1997) utilise an estimation of $\mu = 0.25$ per PWID per year. Moreover, they consider two reasons, AIDS related reasons and other reasons, why infected PWIDs might cease injecting. The authors expect that a fraction 0.125 of PWIDs every year will leave the population for non-HIV related reasons and a separate fraction 0.125 will leave the population because of AIDS related factors. Information presented by Corson (2011) and Corson et al. (2012) is used where the rate that PWIDs leave the PWID population $\mu = 0.17$ per PWID per year which depends on demonstrated evaluations from Hutchinson et al. (2006a) applied to Glasgow PWIDs during the 2000s and utilized

mortality of and cessation of injecting by PWIDs.

The Advisory Council on the Misuse of Drugs (2009) reports that the likelihood of getting contaminated with HCV in the wake of utilizing a infected syringe ranges from $1.5-5\%$. This information can be traced back to research presented by Vickerman et al. (2009) which accepted one transmission likelihood for both acute and chronic HCV disease extending from $1.5-14\%$. Vickerman et al. (2007) affirm an alternate likelihood for the disease transmission for chronic and acute HCV while demonstrating the spread of HCV among PWIDs in London, UK. The initial transmission likelihood for chronic HCV disease ran from $0.84-10\%$ with a multiplier factor for the transmission likelihood of HCV during the acute stage given by one to ten. Further, according to Corson (2011) and Corson et al. (2012) we estimate that $\alpha_h = 0.0432$ and $\alpha_y = 0.016$.

The acute period of infection was taken to be the initial a half year after disease was introduced (Vickerman et al. (2007, 2009)). Subsequently, it was evaluated that $(1/\sigma) = 0.5$ years or $\sigma = 2$ per year. While most people clear their acute HCV disease in this half year time frame, it has been reported that acute disease has lasted as long as two years after starting infection (Cox et al. (2005) and Larghi et al. (2002)).

Past work that has modelled an immune state includes Vickerman et al. (2007, 2009). Vickerman et al. (2007) expect that a fraction of PWIDs, running from 18-50%, can resolve their underlying HCV disease and after a time of acute HCV infection these become immune forever. Due to the uncertainty in evaluating this parameter, Vickerman et al. (2009) assessed that the extent of PWIDs who become immune could go from $0-100\%$. In this perspective, we choose $\alpha = 0.25$ as in Corson (2011) and Corson et al. (2012).

Since most of acute HCV diseases are asymptomatic and accordingly go undiscovered it tends to be hard to precisely measure the proportion of PWIDs that spontaneously resolve HCV infection. Hutchinson et al. (2006a) accept that this extent is in the range 15-40%, with a comparable measure of between 18-50% utilised by Vickerman et al. (2007). Further, $\delta = 0.26$ is used here dependent on an efficient survey of longitudinal examinations including 675 subjects (Micallef et al. 2006).

Fraser et al. (2018) estimate that in Scotland if chronic infections were treated by 2.5% annually therefore the prevalence of HCV will be decreased up to 23.5%. Martin et al. (2011) consider a model in which up to 6% of continuing PWIDs were treated annually. This is in line with observed treatment rates in the UK up to 2015 where at most 3% of PWIDs were treated annually (Martin et al., 2015). Scott et al. (2018) discuss a mathematical model to investigate HCV elimination in line with WHO targets in Iceland, using a complex mathematical model. The model estimated that an 80% reduction in domestic HCV incidence was achievable by 2030, 2025, or 2020 if at least 5.5%, 7.5% and 18.8% of PWIDs were treated per year. However treatments for HCV have improved dramatically in recent years moving from relatively expensive and ineffective interferon based treatments to much more effective and cheaper Directly Acting Antiviral (DAA) treatments. So recently there has been a huge increase in the number of PWIDs being treated (Harris et al. (2019) and Traeger et al.). Traeger et al. (2020) state that in Australia DAAs have moved from a cumulative total of less than 1% of RNA tested PWIDs receiving treatment to a cumulative total of around 45% of RNA tested PWIDs (note that this is RNA tested PWIDs not all PWIDs). Moreover World Health Organization forward targets are even more ambitious with 80% of PWIDs to receive treatment by 2030 (WHO, 2020). Hence we increase the number of continuing PWIDs treated annually from the 0-6% used in Martin et al. (2011) to 10% thus taking $\psi = 0.1$ per year.

Note that a needle that was originally infected becomes uninfected due to time lapsed since injection. But the effect of this would be to have an extra rate at which infected needles became uninfected therefore could be incorporated in the needle turnover rate. However as most other models of the spread of HCV amongst PWIDs do not do this and we do not have data on the rate at which needles become uninfected we have decided not to do this.

Table 3.1: Table of parameter estimates (Adapted from Corson (2011)).

Parameter	Definition	Estimate
ϕ	Probability that a PWID cleans needle	0.255
λ	Needle and syringe sharing rate	103 per year
τ	Needle turnover rate	133 per year
γ	PWIDs to needle ratio	1.002
μ	Per capita rate at which PWIDs leave the sharing, injecting population.	0.17 per PWID per year
α_h	Probability of transmission on the acute stage	0.0432
α_y	Probability of transmission on the chronic stage	0.016
$1/\sigma$	Average duration of the acute stage	0.5 years
δ	Proportion of PWIDs who resolve HCV infection	0.26
α	Proportion of PWIDs that develop immunity	0.25
ψ	Per capita treatment rate	0.1 per year

3.3 Simulation results

3.3.1 Determining R_0

We now use Wolfram Mathematica version 11.1 to produce HCV prevalence estimates for the PWID population in Glasgow, Scotland, over time, given by our model governing equations. The model was comprehensively verified using detailed output from a large number of runs. We do not possess our own source of data from which to estimate the parameters in these models. Instead we rely on parameter estimates from existing published work. Using the baseline set of parameters estimates given in Table 3.1 we estimated that $R_0 = 2.9987 > 1$ which includes intervention measures such as needle exchange and needle cleaning. Note that this value of R_0 is bigger than the one obtained for Corson's model (which was $R_0 = 2.82$). This is because we have introduced treatment of infected PWIDs needle interaction assumptions from the optimistic PWID needle interaction assumptions of Corson (2011) and Corson et al. (2012) to the pessimistic PWID needle interaction assumptions of Lewis and

Greenhalgh (2001). Changing the PWID needle interaction assumptions increases R_0 and this more than offsets the reduction due to introducing treatment of PWIDs. The parameters τ, μ and γ were estimated from Glasgow survey data. δ is estimated to be 0.26 based on a systematic review of longitudinal studies involving 675 subjects (Micallef et al., 2006). We follow Corson (2011) and conservatively estimate $\alpha = 0.25$. We use parameter estimates for α_h and α_y taken from the literature (Kamal et al. (2001) and Villano et al. (1999)). We estimate $\sigma = 0.2$ per year because we follow Vickerman et al., (2007, 2009) and take the acute stage of infection to be the first six months after initial infection. We have increased the number of PWIDs who are treated annually from the 0-6% used in Martin et al. (2011) to 10% thus considering $\psi = 0.1$ per year.

We estimate the transmission of HCV in our model when $R_0 = 2.9987$ over a period of 70 years. It was assumed that one percent of the PWID population were infected with acute HCV (h_1) and no different PWIDs or needles are infected. That is, $\pi_x(0) = 0.99$, $\pi_{x_1}(0) = 0$, $\pi_{h_1}(0) = 0.01$, $\pi_{h_2}(0) = 0$, $\pi_y(0) = 0$, $\pi_z(0) = 0$ and $\beta_{h_1}(0) = \beta_{h_2}(0) = \beta_y(0) = 0$ where $\pi_x(0)$ means the division of PWIDs in the x-susceptible class at time t=0 and likewise for all other PWID and needles classes for the two assumptions. The prevalence of HCV in the PWID population (we follow Corson (2011) and we use the Health Protection Scotland meaning of those testing HCV antibody positive, which is given by $\pi_{x_1} + \pi_{h_1} + \pi_{h_2} + \pi_y + \pi_z$), as well as the infectious needles, are illustrated in Figure 3.1. Time is measured in years.

It is obvious from the figure that the division of PWIDs and needles infected with HCV in the end arrives at a steady state solution. The steady state values for PWIDs in each phase of disease are

$$(\pi_x^*, \pi_{x_1}^*, \pi_{h_1}^*, \pi_{h_2}^*, \pi_y^*, \pi_z^*) = (0.3497, 0.0523, 0.0610, 0.0214, 0.4524, 0.0631).$$

Similarly, for needles at every phase of disease, the rough steady state values in Assumption 1 are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0.03843, 0.01298, 0.22401)$. Additionally, for Assumption 2 the quantities are $(\beta_{h_1}^*, \beta_{h_2}^*, \beta_y^*) = (0.03799, 0.01301, 0.22382)$. This compares to an endemic HCV prevalence of $\pi^* = 0.5348$ for needle and syringe sharing PWIDs in Glasgow and $\beta^* = 0.275$ for needles in the two assumptions, where $\pi^* = \pi_{h_1} + \pi_{h_2} + \pi_y$ and $\beta^* = \beta_{h_1}^* + \beta_{h_2}^* + \beta_y^*$. We have given the simulation

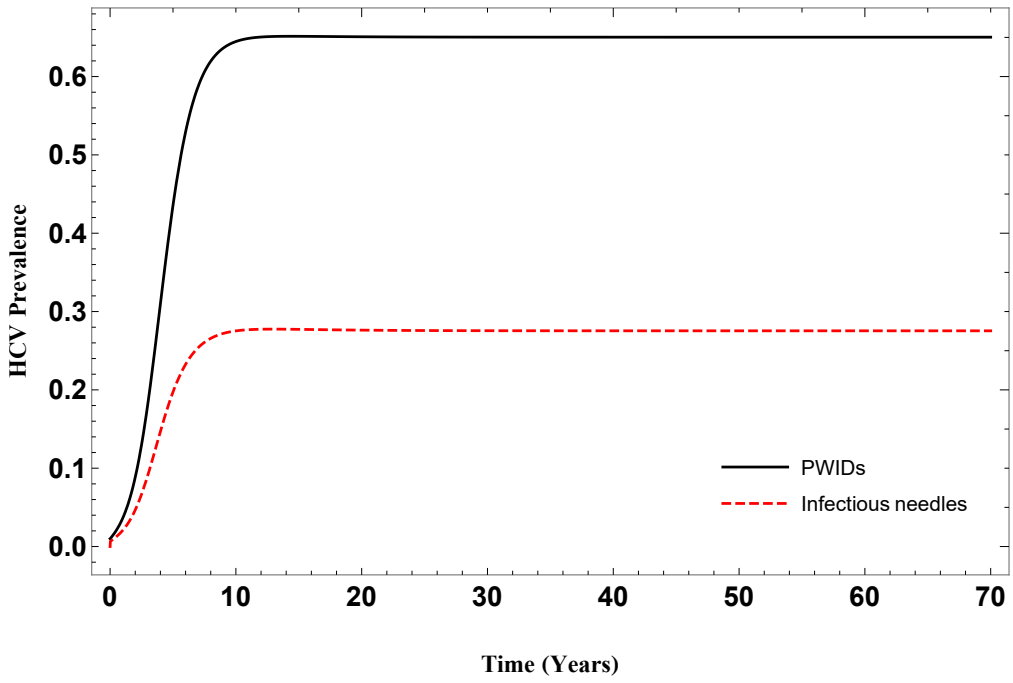

Figure 3.1: HCV prevalence among Glasgow needle and syringe sharing PWIDs (solid black line) and infectious needles (dashed red line) when $R_0 = 2.9987$ for Assumption one.

results over a long period of time so that we can demonstrate the analytical results that the system tends to an endemic equilibrium. However practitioners would be more interested in results over a shorter timescale.

3.4 Threshold parameter values such that $R_0 \leq 1$

Analytical determination of critical values

We are following a similar technique in Corson (2011) and Corson et al. (2012) to calculate ϕ_{crit}, λ_{crit}, τ_{crit} and ψ_{crit}. Hence using equation (2.3.13) and Table 3.1, then we can find values for each of λ, ϕ, τ and ψ, keeping all other parameters constant, that the outcomes result in $R_0 = 1$ and hence eliminate HCV.

Definition 3.4.1. *Similarly to Corson (2011) we define*

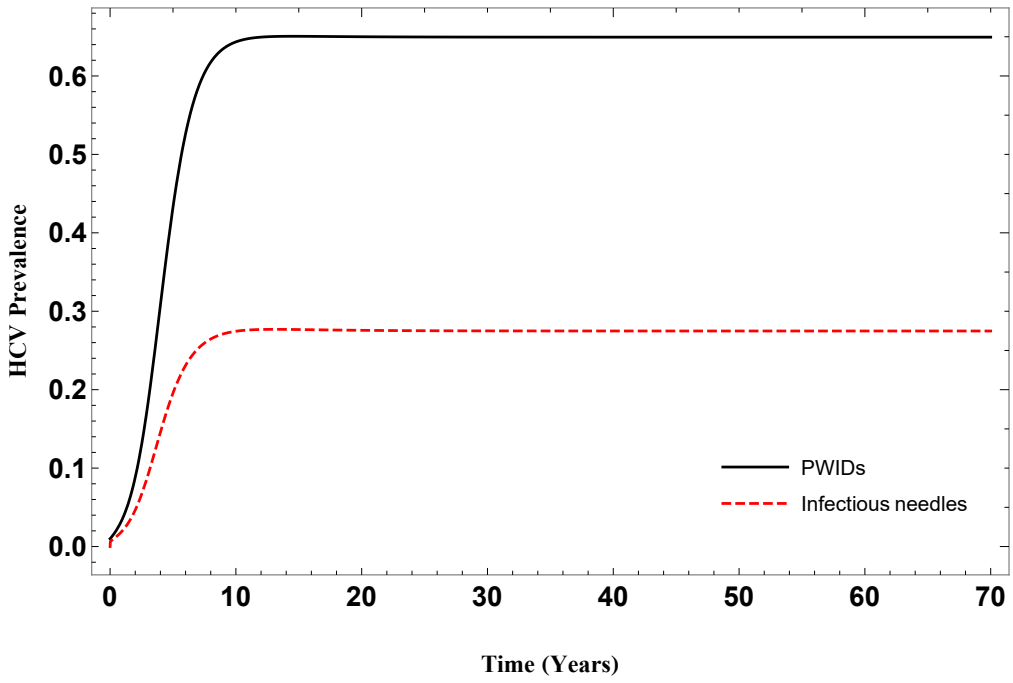

Figure 3.2: HCV prevalence among Glasgow needle and syringe sharing PWIDs (solid black line) and infectious needles (dashed red line) when $R_0 = 2.9987$ for Assumption two.

(i) λ_{crit} *refers to the unique critical value of* λ *which leads to* $R_0 \leq 1$ *when* $\lambda \leq \lambda_{crit}$*;*

(ii) ϕ_{crit} *refers to the unique critical value of* ϕ *which leads to* $R_0 \leq 1$ *when* $\phi \geq \phi_{crit}$*;*

(iii) τ_{crit} *refers to the unique critical value of* τ *which leads to* $R_0 \leq 1$ *when* $\tau \geq \tau_{crit}$*;*

(iv) ψ_{crit} *refers to the unique critical value of* ψ *which leads to* $R_0 \leq 1$ *when* $\psi \geq \psi_{crit}$*.*

We shall show later that these values $\lambda_{crit}, \phi_{crit}, \tau_{crit}$ and ψ_{crit} do exist and are unique.

3.4.1 Determining λ_{crit}

From previous chapter we have noted that R_0 is a monotone increasing function of λ. Therefore to set the critical value of λ we start with the expression for R_0 obtained in Chapter 2 with $R_0 = 1$ and $\lambda = \lambda_{crit}$. Following Corson (2011) this leads to

$$1 = \frac{\lambda_{crit}(1-\phi)}{(\mu+\psi)(\mu+\sigma)(\phi+\hat{\tau})}[(\mu+\psi)\alpha_h + \alpha_y\sigma(1-\delta)] \tag{3.4.1}$$

where $\hat{\tau} = \frac{\tau}{\lambda_{crit}\gamma}$.

Re-arranging (3.4.1), for λ_{crit} gives

$$\frac{(0.0449416)\lambda_{crit}}{\left(0.255 + \frac{133.266}{\lambda_{crit}}\right)} = 1.$$

Solving this equation we have $\lambda_{crit} = 57.4$. We summarise that a needle and syringe sharing rate of $\lambda \leq \lambda_{crit} = 57.4$ per year gives $R_0 \leq 1$ and therefore eventual HCV elimination in all PWIDs and needles. To contrast this value with λ_{crit} in Corson's model which is less than ours:

$$\begin{aligned}
&\lambda_{crit} = 54.7 \text{ per year}, \quad \text{(Corson (2011) and Corson et al. (2012))},\\
&\lambda_{crit} = 48.1 \text{ per year}, \quad \text{(our model with } \psi = 0.0 \text{ per year)},\\
&\lambda_{crit} = 57.4 \text{ per year}, \quad \text{(our model with } \psi = 0.1 \text{ per year)}.
\end{aligned}$$

Note that the λ_{crit} in Corson's model is bigger than ours if there is no treatment and this effect is because that we are changing the PWID needle interaction assumptions from optimistic to pessimistic. In contrast when we have not introduced treatment of infected PWIDs, which we would expect to increase λ_{crit}, therefore treatment of infected PWIDs does indeed increase λ_{crit} to larger than Corson's model.

3.4.2 Determining ϕ_{crit}

Following Corson (2011) we are now going to calculate the level of successful needle and syringe cleaning that gives outcomes of $R_0 \leq 1$ and HCV elimination in all PWIDs and needles. We again begin with the expression for R_0 but with ϕ changed to ϕ_{crit}:

$$1 = \frac{\lambda(1-\phi_{crit})}{(\mu+\psi)(\mu+\sigma)(\phi_{crit}+\hat{\tau})}[(\mu+\psi)\alpha_h + \alpha_y\sigma(1-\delta)] \tag{3.4.2}$$

where $\hat{\tau} = \frac{\tau}{\lambda\gamma}$.

Re-arranging (3.4.2), again put $\psi = 0.0$ per year as Corson (2011), for ϕ_{crit} gives

$$\frac{(6.213)(1-\phi_{crit})}{(1.29384+\phi_{crit})} = 1.$$

Solving this equation we have $\phi_{crit} = 0.682$. Again by contrasting this value with ϕ_{crit} in Corson's model which is bigger than ours (ignoring treatment):

$$\phi_{crit} = 0.736, \quad \text{(Corson (2011) and Corson et al. (2012))},$$
$$\phi_{crit} = 0.763, \quad \text{(our model with } \psi = 0.0 \text{ per year)},$$
$$\phi_{crit} = 0.682, \quad \text{(our model with } \psi = 0.1 \text{ per year)}.$$

Note that our value of ϕ_{crit} is less than the value of ϕ_{crit} obtained by Corson (2011) and Corson et al. (2012) when we have considered treatment this is because we have also changed the PWID needle interaction assumptions from optimistic to pessimistic but when we have not introduced treatment of infected PWIDs, which we would expect to increase ϕ_{crit}, therefore the value of ϕ_{crit} is larger than the value of ϕ_{crit} obtained by Corson (2011) and Corson et al. (2012).

3.4.3 Determining τ_{crit}

Again we are now following Corson (2011) to calculate the average needle turnover rate that gives $R_0 \leq 1$. We again start with the expression for R_0 but with τ changed to τ_{crit}:

$$1 = \frac{\lambda(1-\phi)}{(\mu+\psi)(\mu+\sigma)(\phi+\hat{\tau}_{crit})}[(\mu+\psi)\alpha_h + \alpha_y\sigma(1-\delta)] \tag{3.4.3}$$

where $\hat{\tau}_{crit} = \frac{\tau_{crit}}{\lambda\gamma}$.

After substituting in the necessary parameter values we get that $\tau_{crit} = 449.621$ per year. Moreover by comparing this value with τ_{crit} in Corson's model which is bigger than ours:

$$\tau_{crit} = 562 \text{ per year}, \quad \text{(Corson (2011) and Corson et al. (2012))},$$
$$\tau_{crit} = 637.152 \text{ per year}, \quad \text{(our model with } \psi = 0.0 \text{ per year)},$$
$$\tau_{crit} = 449.621 \text{ per year}, \quad \text{(our model with } \psi = 0.1 \text{ per year)},$$

then we summarise that τ_{crit} for Corson's model is bigger than to τ_{crit} for our model which is considering treatment. Again note that we have changed the PWID needle interaction assumptions from optimistic to pessimistic but when we have not considered treatment then the τ_{crit} for Corson's model is less than τ_{crit} for our model. Hence we have summarised these results in Table 3.2.

	λ_{crit} (per year)	ϕ_{crit}	τ_{crit} (per year)
Our model estimate with $\psi = 0.0$ per year	48.1077	0.763	637.152
Corson's estimate	54.7	0.736	562.82
Our model estimate with $\psi = 0.1$ per year	57.4	0.682	449.621

Table 3.2: Comparison of the critical values for λ, ϕ and τ between Corson's model and our model.

3.4.4 Determining ψ_{crit}

We are now going to calculate the level of rate of treatment that gives outcomes of $R_0 \leq 1$ and HCV elimination in all PWIDs and needles. We again begin with the expression for R_0 but with ψ changed to ψ_{crit}:

$$1 = \frac{\lambda(1-\phi)}{(\mu+\psi_{crit})(\mu+\sigma)(\phi+\hat{\tau})}[(\mu+\psi_{crit})\alpha_h + \alpha_y\sigma(1-\delta)] \tag{3.4.4}$$

where $\hat{\tau} = \frac{\tau}{\lambda\gamma}$.

Solving (3.4.4) for ψ_{crit} then we have $\psi_{crit} = 39.296$ per year of PWIDs are treated per year.

We have assumed that these parameters are independent of one another. In reality these parameters are influenced by both biological factors and sociological factors and it may be that because of the sociological factors there is some interdependence between some of these parameters. However this would be very complicated to model and it is still useful to focus on one parameter at a time to influence the relative impact of different control policies which could potentially influence one factor at a time.

3.5 The effect of treatment on the prevalence estimates

In this subsection, we will look at the changed model practises which result from different ψ parameters for long term HCV prevalence. We run simulations utilizing three unique estimations of ψ relating to our present parameter value ($\psi = 0.03$ per

year), which was estimated by Martin et al. (2015), ($\psi = 0.06$ per year) which was estimated by Martin et al. (2011) and our estimation which is ($\psi = 0.1$ per year). As Corson (2011) did not consider treatment this is different to his thesis.

Figures 3.3 and 3.4 show the subsequent HCV prevalence levels for both PWIDs and needles. To show the impacts of these progressions all the more obviously we have given the endemic equilibrium values in both PWIDs and needles in Table 3.3.

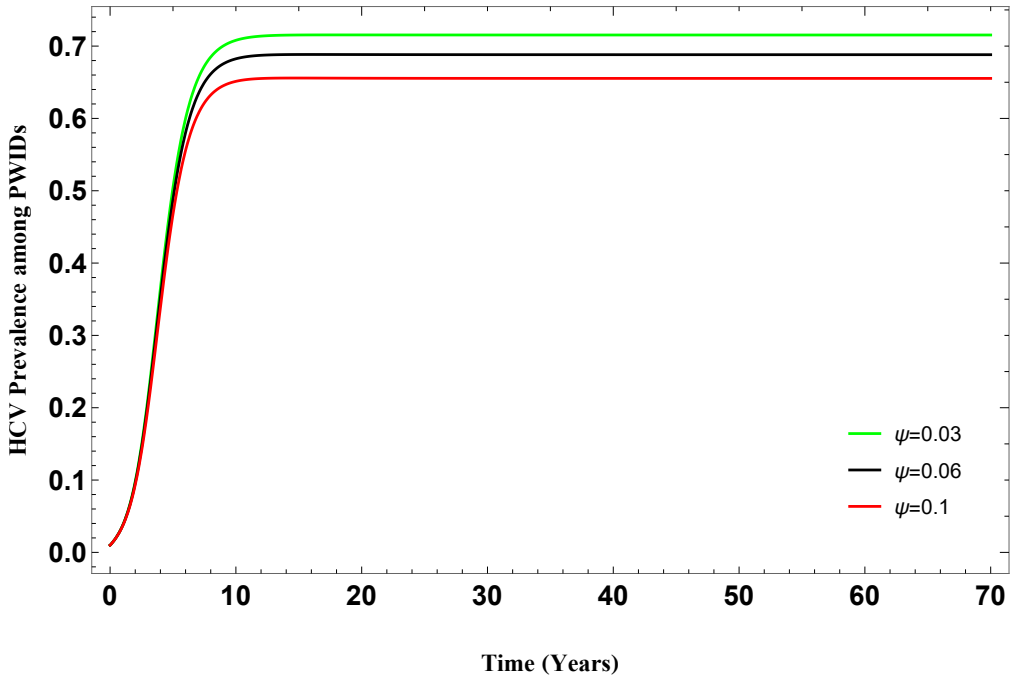

Figure 3.3: HCV prevalence among sharing PWIDs with $\psi = 0.03, 0.06$ and 0.1 per year.

From these simulations we can see that increasing the rate of treatment causes a decrease in the prevalence but it is relatively small compared with other interventions.

ψ	Prevalence among sharing PWIDs	Prevalence among shared needles
0.03	0.715	0.324
0.06	0.688	0.312
0.1	0.655	0.297

Table 3.3: Endemic equilibrium HCV prevalence for sharing PWIDs and needles with $\psi = 0.03, 0.06$ and 0.1 per year.

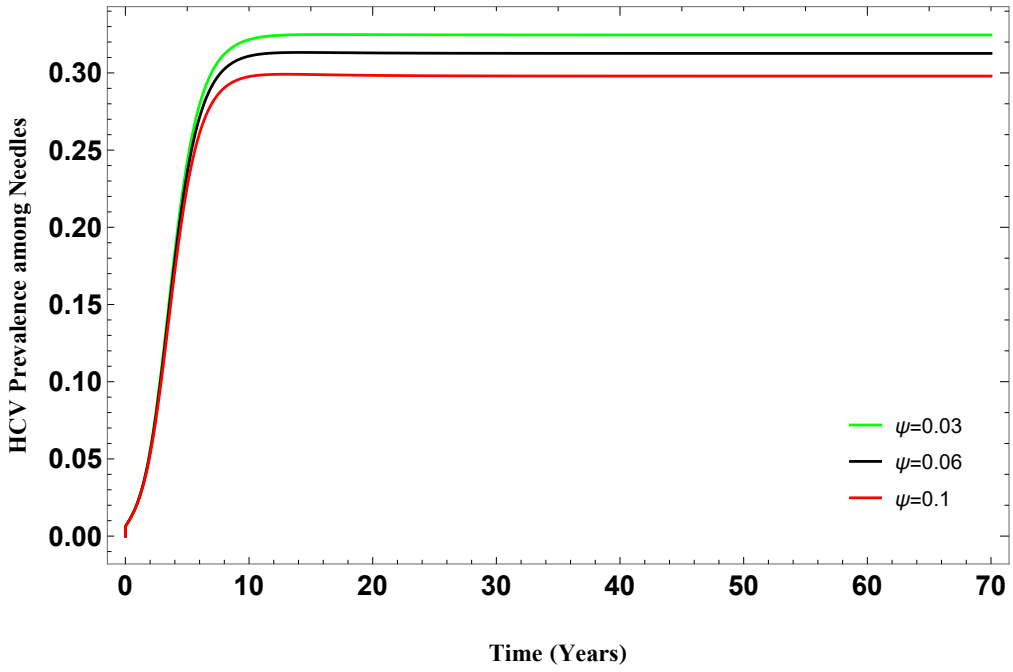

Figure 3.4: HCV prevalence among shared needles with $\psi = 0.03, 0.06$ and 0.1 per year.

3.6 Comparison between our simulation results without considering treatment and the results of Corson (2011)

As we have shown in previous chapter, our model is similar to the 'Pessimistic Model' of HIV transmission amongst PWIDs studied by Lewis and Greenhalgh (2001a) and Corson's model is similar to the 'Optimistic Model' studied by Greenhalgh and Lewis

λ (per year)	92.7	103	113
Our model results with $\psi = 0$ per year	0.689	0.738	0.776
Results of Corson (2011)	0.629	0.689	0.735
Difference	6%	4.9%	4.1%

Table 3.4: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different λ between the model of Corson (2011) and our model with $\psi = 0$ per year.

(2000). Therefore we expect that disease will spread faster in our model so more control effort will be needed.

Table 3.4 to Table 3.9 respectively give the results under the pessimistic scenario when each of the different parameters λ, ϕ, τ, α_y, α_h and δ is varied keeping the other parameters constant. From these tables it is clear that the endemic equilibrium of HCV prevalence among PWIDs is bigger in our model than in Corson (2011). In Table 3.4 where the parameter λ is increased from 92.7 per year to 113 per year then the difference in the endemic equilibrium HCV prevalence amongst PWIDs is decreased from 6% to 4%. Moreover in Table 3.5 when the parameter ϕ is increased from 0.255 to 0.3825 then the difference in the endemic equilibria increases from 4.9% to 5.5% and in Table 3.6 when the parameter τ increases from 133 per year to 199.5 per year then the difference in the endemic equilibria increases from 4.9% to 5.8%. A similar scenario happens in Tables 3.7 and 3.8 which consider the parameters α_y and α_h respectively. The difference in the endemic equilibrium prevalence amongst PWIDs decreases from 4.9% when $\alpha_y = 0.0160$ to 0.8% when $\alpha_y = 0.0432$ and from 5.2% when $\alpha_h = 0.016$ to 3.9% when $\alpha_h = 0.14$. Also in Table 3.9 when the difference in endemic equilibria increases from 4% when $\delta = 0.15$ to 8.1% when $\delta = 0.5$.

ϕ	0.255	0.2805	0.306	0.3825
Our model results with $\psi = 0$ per year	0.738	0.727	0.716	0.675
Results of Corson (2011)	0.689	0.678	0.665	0.620
Difference	4.9%	4.9%	5.1%	5.5%

Table 3.5: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different ϕ between the model of Corson (2011) and our model with $\psi = 0$ per year.

τ (per year)	133	146.35	159.6	199.5
Our model results with $\psi = 0$ per year	0.738	0.721	0.704	0.652
Results of Corson (2011)	0.689	0.671	0.652	0.594
Difference	4.9%	5%	5.2%	5.8%

Table 3.6: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different τ between the model of Corson (2011) and our model with $\psi = 0$ per year.

α_y	0.0160	0.0296	0.0432
Our model results with $\psi = 0$ per year	0.738	0.834	0.878
Results of Corson (2011)	0.689	0.817	0.870
Difference	4.9%	1.7%	0.8%

Table 3.7: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different α_y between the model of Corson (2011) and our model with $\psi = 0$ per year.

α_h	0.016	0.026	0.0432	0.05	0.14
Our model results with $\psi = 0$ per year	0.682	0.705	0.738	0.749	0.841
Results of Corson (2011)	0.630	0.655	0.689	0.701	0.802
Difference	5.2%	5%	4.9%	4.8%	3.9%

Table 3.8: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different α_h between the model of Corson (2011) and our model with $\psi = 0$ per year.

δ	0.15	0.26	0.5
Our model results with $\psi = 0$ per year	0.745	0.738	0.713
Results of Corson (2011)	0.705	0.689	0.632
Difference	4%	4.9%	8.1%

Table 3.9: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different δ between the model of Corson (2011) and our model with $\psi = 0$ per year.

3.7 Comparison between our simulation results with $\psi = 0.1$ per year and the results of Corson (2011)

We have seen that disease will spread faster in our model without treatment than in the model of Corson (2011) but in this section we have introduced treatment so it is no longer clear whether or not disease will spread faster in our model.

Table 3.10 to 3.15 respectively again give the results under the pessimistic scenario when each of the different parameters λ, ϕ, τ, α_y, α_h and δ is varied keeping the other parameters constant. From these tables it is clear that the endemic equilibria of HCV prevalence among PWIDs are larger in the model of Corson (2011) than our model with $\psi = 0.1$ per year. In Table 3.10 where the parameter λ is increased from 92.7 per year to 113 per year then the difference in the endemic equilibrium

λ (per year)	92.7	103	113
Results of Corson (2011)	0.629	0.689	0.735
Our model results with $\psi = 0.1$ per year	0.584	0.650	0.699
Difference	4.5%	3.9%	3.6%

Table 3.10: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different λ between the model of Corson (2011) and our model with $\psi = 0.1$ per year.

ϕ	0.255	0.2805	0.306	0.3825
Results of Corson (2011)	0.689	0.678	0.665	0.620
Our model results with $\psi = 0.1$ per year	0.650	0.636	0.621	0.563
Difference	3.9%	4.2%	4.4%	5.7%

Table 3.11: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different ϕ between the model of Corson (2011) and our model with $\psi = 0.1$ per year.

HCV prevalence amongst PWIDs is decreased from 4.5% to 3.6%. Also in Table 3.11 when the parameter ϕ is increased from 0.255 to 0.3825 then the difference in the endemic equilibria increases from 3.9% to 5.7% and in Table 3.12 when the parameter τ increases from 133 per year to 199.5 per year then the difference in the endemic equilibria increases from 3.9% to 6.2% and a similar scenario happens in Table 3.13 when the difference in endemic equilibria increases from 3.9% when $\alpha_y = 0.0.0160$ to 4.6% when $\alpha_y = 0.0432$. Moreover, in Tables 3.14 and 3.15 which consider the parameters α_h and δ respectively the difference in the endemic equilibrium prevalence among PWIDs decreases from 8.2% when $\alpha_h = 0.0160$ to 0.9% when $\alpha_h = 0.14$ and from 5% when $\delta = 0.15$ to 0.5% when $\delta = 0.5$.

τ (per year)	133	146.35	159.6	199.5
Results of Corson (2011)	0.689	0.671	0.652	0.594
Our model results with $\psi = 0.1$ per year	0.650	0.627	0.603	0.531
Difference	3.9%	4.4%	4.9%	6.2%

Table 3.12: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different τ between the model of Corson (2011) and our model with $\psi = 0.1$ per year.

α_y	0.0160	0.0296	0.0432
Results of Corson (2011)	0.689	0.817	0.870
Our model results with $\psi = 0.1$ per year	0.650	0.766	0.824
Difference	3.9%	5.1%	4.6%

Table 3.13: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different α_y between the model of Corson (2011) and our model with $\psi = 0.1$ per year.

α_h	0.016	0.026	0.0432	0.05	0.14
Results of Corson (2011)	0.630	0.655	0.689	0.701	0.802
Our model results with $\psi = 0.1$ per year	0.548	0.591	0.650	0.670	0.793
Difference	8.2%	6.4%	3.9%	3.1%	0.9%

Table 3.14: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different α_h between the model of Corson (2011) and our model with $\psi = 0.1$ per year.

δ	0.15	0.26	0.5
Results of Corson (2011)	0.705	0.689	0.632
Our model results with $\psi = 0.1$ per year	0.655	0.650	0.627
Difference	5%	3.9%	0.5%

Table 3.15: Comparison of endemic equilibrium HCV prevalence among sharing PWIDs for different δ between the model of Corson (2011) and our model with $\psi = 0.1$ per year.

3.7.1 Conclusion and discussion

In this chapter, the consequences of the simulations affirmed analytical results and permitted us to use the model to gauge the degree of interventions required to achieve $R_0 \leq 1$ and in this way wipe out HCV in all PWIDs and needles. Investigative strategies have led to the inference of the critical values of needle and syringe sharing rates (λ), needle cleaning (ϕ), needles turnover (τ) and rate of treatment (ψ) that are expected to achieve $R_0 \leq 1$. The examination, which was confirmed by simulations, shows that given that every single other parameter stays fixed each separately of $\lambda \leq 48.10$ per year, $\phi \geq 0.76$, $\tau \geq 637.152$ per year and $\psi \geq 39.296$ per year results in $R_0 \leq 1$ and possible HCV elimination in PWIDs and needles. For the model with $\psi = 0$ per year the pessimistic assumptions make the endemic equilibrium prevalence higher but introducing treatment brings it down again. However for realistic parameter values the effects of treatment seem to be small, even if we increase the treatment levels beyond the values used in previous simulations. This supports WHO recommendations of very high treatment levels necessary.

In summary, this study has created and explored a numerical model that approximates the spread of HCV among PWIDs, and in spite of various assumptions which are capable of being improved, we have acquired sensible prevalence estimates. Moreover, this study has indicated that focused interventions can diminish HCV prevalence among the Glasgow PWID population. Our model differs from that of Corson (2011) and Corson et al. (2012) in that we introduce treatment of infected PWIDs at rate ψ and assume that needles cannot lose infectiousness over

time. We have compared our results with those of Corson (2011) when we have introduced treatment and without treatment.

Chapter 4

A Time Since First Injection Model for the Spread of HCV Amongst PWIDs

In this chapter, we develop a mathematical model aimed at creating two groups within the PWID population participating in this research. These two groups will be named naive and experienced PWIDs. The distinction between the two will be made by period of time since their first injection (Corson (2011) and Corson et al. (2013)). The first step requires us to describe the model and the assumptions made that would allow PWIDs to progress along various stages of HCV infection. This step is followed by the derivation of a basic reproduction number R_0 that pre-empts the analysis of the model mathematically. The model behaviour is controlled by the basic reproduction number, we shall demonstrate that when $R_0 \leq 1$, and HCV is initially present in the population, the system will tend towards the globally asymptotically stable DFE where HCV has been eliminated from the population. After that, we study the behaviour of this model numerically.

4.1 Model description

The model of Corson (2011) and Corson et al. (2013) discussed a mathematical model which separate a PWID population into two different groups (naive and experienced) by their time since first injection.

This model description is based on Corson (2011) and Corson et al. (2013) except that the PWID needle interactions follow the assumptions made in Chapter 2 so every time that a PWID injects with a needle the needle takes on the infectious disease characteristics of that PWID, also chronically infected PWIDs are treated at per capita rate ψ. However we shall shortly see that some of the mathematics is very different and much more complicated than that model. For this research, a modified version of the model in Chapter Two is applied. This model focuses on the PWID only group of participants and does not overtly focus on needles. It divides the participant group of the PWID population into two risk groups based on the beginning of injection practice. This work bases its methods and practices on models by Greenhalgh and Hay (1997), Kretzchmar and Wiessing (2004), Vickerman et al. (2009), Corson (2011) and Corson et al. (2013).

To explore this issue, the modified model will separate the test PWID participants into two risk groups. These groups will be namely naive and experienced PWIDs. This distinction will be made by their individual injection times and also incorporate the prevention measures that aim to prevent further HCV infection (Corson (2011) and Corson et al. (2013)). In this model, we consider the outcome of HCV antiviral treatment on PWIDs.

This model relies on the assumption that is used in Corson (2011) and Corson et al. (2013) in which the PWID population selected is of size n, where n is a large number and remains constant. These assumptions therefore imply that PWIDs who stop injecting drugs due to ceasing injecting drug use or death leave the population under consideration at an individual rate μ. This translates to a phenomenon where each individual to leave is replaced by an individual among the PWID population susceptible to HCV infection.

Again as assumed in Corson (2011) and Corson et al. (2013) the modified

model to be applied here also allows for several HCV infection stages. These stages are individuals susceptible to infection, (represented by x for those not previously infected and x_1 for those previously infected), individuals acutely infected with HCV (denoted h_1 and h_2), individuals chronically infected (y) and finally individuals who are immune to HCV re-infection (z). In a later section, the term f_i, will be defined to denote the impact of infection among naive ($i = 0$) and experienced PWIDs ($i = 1$) accordingly.

While susceptible PWIDs are infected with HCV they then move on to another level that is acute stage of infection (either h_1 or h_2). A proportion δ of newly infected PWIDs move to this acute h_2 infected level. Eventually, the individuals in this category either leave the injecting group of participants or clear their infection. Of those that clear their infection there is however a fraction α that develop an immunity to HCV re-infection alongside another fraction $(1 - \alpha)$ that remains susceptible to HCV re-infection (Farci et al. (1992), Mehta et al. (2002) and Micallef et al. (2007)). The remaining fraction of $(1 - \delta)$ of newly infected PWIDs cross over to the acute h_1 infected class which leads to either leaving the sharing, injecting population or the development of chronic HCV. Once chronically infected, the PWID participants remain infected until death or until they eventually leave the injecting population.

When separating the PWID population according to infection status, this modified model further separates the participant PWIDs into two groups. These two group numbers vary depending on whether the individuals have a short (naive) or long (experienced) injecting career. Every naive PWID participant moves at an individual rate η from the novice level to the experienced level which is represented in a shift from one group to the other. Through this shift, these particular individuals cross over into an equivalent model category that corresponds to their present HCV infection condition.

4.2 Model derivation

We now derive the differential equations which describe the spread of HCV among PWIDs where PWIDs progress through the stages of infection described in the previous section. We first use techniques used previously to derive a model where both PWIDs and needles are modelled explicitly. If we assume that needles can be either naive or experienced (with two PWID-needle interaction assumptions as in the simple model) 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 PWIDs and six for needles for Assumption 1 and 12 equations for PWIDs and six for needles for Assumption 2. We then derive a PWID only model and show that under certain conditions these models are equivalent in the sense that by the quasi-steady-state argument used earlier, the PWID only model would be expected to approximate the model with PWIDs and needles and also the models have the same basic reproduction number and equilibrium values. A total of 12 differential equations will be derived for the PWID only model.

Consider $\pi_x^i(t)$, $\pi_{x_1}^i(t)$, $\pi_{h_1}^i(t)$, $\pi_{h_2}^i(t)$, $\pi_y^i(t)$ and $\pi_z^i(t)$ to represent the fraction of PWIDs 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. Also $\beta_{h_1}^i(t)$, $\beta_{h_2}^i(t)$ and $\beta_y^i(t)$ respectively represent the fraction of needles and syringes that were last used by a naive ($i = 0$) or experienced ($i = 1$) user.

Furthermore, λ_i denotes the value of the needle and syringe sharing rates in the i'th group of PWIDs. ϕ then indicates the likelihood that a particular PWID thoroughly disinfects their needles and syringes before use (meaning that PWIDs disinfect injecting paraphernalia using alcohol or bleach to remove all HCV viral load before injecting themselves). α_h and α_y denote the transmission of acute and chronic HCV infection, respectively. s_{i0} and s_{i1} then show the portion of the injecting apparatus a naive ($i = 0$) or experienced ($i = 1$) PWID borrows from naive and experienced injecting PWIDs, respectively.

Finally π^0 and π^1 denote the fractions of naive and experienced PWIDs, respectively. Henceforth, we will assume that this constraint is satisfied. If we are

consider the fraction of naive $\pi^0(t)$ and experienced $\pi^1(t)$ drug users at time t we have

$$\frac{d\pi^0}{dt} = \mu - (\mu + \eta)\pi^0 \tag{4.2.1}$$

and

$$\frac{d\pi^1}{dt} = \eta\pi^0 - \mu\pi^1. \tag{4.2.2}$$

It is straightforward to show that over time

$$\pi^0(t) \quad \rightarrow \quad \pi_0^* = \frac{\mu}{\mu + \eta}, \tag{4.2.3}$$

$$\pi^1(t) \quad \rightarrow \quad \pi_1^* = \frac{\eta}{\mu + \eta}. \tag{4.2.4}$$

Note that we follow Corson (2011) and Corson et al. (2013) in order to ensure that our model is realistic by putting a constraint on s_{01} and s_{10} by ensuring that $\lambda_0 s_{01}\mu = \lambda_1 s_{10}\eta$. This is necessary to ensure that the number of needles in the two experience groups remains positive. It ensures that at equilibrium the total number of needles borrowed by naive users from the experienced group is equal to the total number of needles borrowed from the naive group by experienced users.

4.2.1 Dynamic equations for PWID and needle model

We now derive the equations which describe the behaviour of our PWID population over time t.

PWID population

Following a similar way as in Corson (2011) and Corson et al. (2013) to derive the PWID equation for naive x-susceptible then we have

The change in the number of naive x-susceptible individuals in the small time interval $[t, t + \triangle t)$

$x^0(t+\triangle t) - x^0(t)$

= new naive x-susceptible PWIDs born in $[t, t+\triangle t)$ i.e. the number of PWIDs recruited to sharing intravenous injecting drug use in $[t, t+\triangle t)$

− the number of naive x-susceptible PWIDs who move into the experienced tier of the model in $[t, t+\triangle t)$

− the number of naive x-susceptible PWIDs who leave the population due to death or cessation of injecting drug use in $[t, t+\triangle t)$

− the number of naive x-susceptible PWIDs who develop acute HCV infection after borrowing needles and syringes last used by naive PWIDs in $[t, t+\triangle t)$

− the number of naive x-susceptible PWIDs who develop acute HCV infection after borrowing needles and syringes last used by experienced PWIDs in $[t, t+\triangle t)$

+ the number of naive y-chronic PWIDs who successfully treat HCV infection in $[t, t+\triangle t)$.

$$= \mu n\triangle t - (\mu+\eta)x^0\triangle t - \triangle t\lambda_0 s_{00}(1-\phi)x^0(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2})+\alpha_y\beta^0_y) - \triangle t\lambda_0 s_{01}(1-\phi)x^0(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2})+\alpha_y\beta^1_y) + \psi y^0\triangle t + o(\triangle t).$$

Dividing both sides by $\triangle t$ then we have

$$\frac{x^0(t+\triangle t)-x^0(t)}{\triangle t} = \mu n - (\mu+\eta)x^0 - \lambda_0 s_{00}(1-\phi)x^0(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2})+\alpha_y\beta^0_y) - \lambda_0 s_{01}(1-\phi)x^0(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2})+\alpha_y\beta^1_y) + \psi y^0 + o(1).$$

Letting $\triangle t \to 0$ we deduce that

$$\frac{dx^0(t)}{dt} = \mu n - (\mu+\eta)x^0 - \lambda_0 s_{00}(1-\phi)x^0(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2})+\alpha_y\beta^0_y) - \lambda_0 s_{01}(1-\phi)x^0(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2})+\alpha_y\beta^1_y) + \psi y^0.$$

Dividing by n, and recalling that $\pi^0_x = \frac{x^0}{n}$, $\pi^0_y = \frac{y^0}{n}$,

$$\frac{d\pi^0_x}{dt} = \mu - (\mu+\eta)\pi^0_x - \lambda_0 s_{00}(1-\phi)\pi^0_x(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2})+\alpha_y\beta^0_y) - \lambda_0 s_{01}(1-\phi)\pi^0_x(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2})+\alpha_y\beta^1_y) + \psi\pi^0_y.$$

The change in the number of naive chronic y infected individuals in the small time interval $[t, t+\triangle t)$ $y^0(t+\triangle t) - y^0(t)$

$=$ the number of naive acute h_1 infected PWIDs that develop chronic HCV infection in $[t, t+\triangle t)$

$-$ the number of chronic cases that leave the sharing, injecting population in $[t, t+\triangle t)$

$-$ the number of chronic cases that move into the experienced tier in $[t, t+\triangle t)$

$-$ the number of naive y-chronic PWIDs who successfully treat HCV infection after borrowing needles and syringes last used by naive PWIDs in $[t, t+\triangle t)$,

$$= n\triangle t\pi^0_{h_1}(t)\sigma - n(\mu+\eta)\pi^0_y(t)\triangle t - \psi\pi^0_y(t)n\triangle t + o(\triangle t).$$

Hence, dividing both sides by $\triangle t$ we have that

$$\frac{y^0(t+\triangle t) - y^0(t)}{\Delta t} = n\pi^0_{h_1}(t)\sigma - n(\mu+\eta)\pi^0_y(t) - \psi\pi^0_y(t)n + o(1).$$

Letting $\triangle t \to 0$ we deduce that

$$\begin{aligned}\frac{dy^0}{dt} &= n\pi^0_{h_1}(t)\sigma - n(\mu+\eta)\pi^0_y(t) - n\psi\pi^0_y(t),\\ &= \pi^0_{h_1}\sigma - (\mu+\eta)\pi^0_y - \psi\pi^0_y.\end{aligned}$$

The derivations of the equations for naive x_1-susceptible, naive acute h_1, naive acute h_2 and naive chronic y are given by

$$\begin{aligned}\frac{d\pi^0_x}{dt} &= \mu - (\mu+\eta)\pi^0_x - \lambda_0 s_{00}(1-\phi)\pi^0_x(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2}) + \alpha_y\beta^0_y)\\ &\quad - \lambda_0 s_{01}(1-\phi)\pi^0_x(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2}) + \alpha_y\beta^1_y) + \psi\pi^0_y,\\ \frac{d\pi^0_{x_1}}{dt} &= \sigma(1-\alpha)\pi^0_{h_2} - (\mu+\eta)\pi^0_{x_1} - \lambda_0 s_{00}(1-\phi)\pi^0_{x_1}(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2})\\ &\quad + \alpha_y\beta^0_y) - \lambda_0 s_{01}(1-\phi)\pi^0_{x_1}(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2}) + \alpha_y\beta^1_y),\\ \frac{d\pi^0_{h_1}}{dt} &= \lambda_0 s_{00}(1-\phi)(1-\delta)\big(\pi^0 - \Sigma_k\pi^0_k\big)(\alpha_h(\beta^0_{h_1}+\beta^0_{h_2}) + \alpha_y\beta^0_y)\\ &\quad + \lambda_0 s_{01}(1-\phi)(1-\delta)\big(\pi^0 - \Sigma_k\pi^0_k\big)(\alpha_h(\beta^1_{h_1}+\beta^1_{h_2}) + \alpha_y\beta^1_y)\\ &\quad - (\mu+\sigma+\eta)\pi^0_{h_1},\end{aligned}$$

$$\begin{aligned}\frac{d\pi^0_{h_2}}{dt} &= \lambda_0 s_{00}(1-\phi)\delta\big(\pi^0 - \Sigma_k \pi^0_k\big)(\alpha_h(\beta^0_{h_1} + \beta^0_{h_2}) + \alpha_y \beta^0_y) \\ &\quad + \lambda_0 s_{01}(1-\phi)\delta\big(\pi^0 - \Sigma_k \pi^0_k\big)(\alpha_h(\beta^1_{h_1} + \beta^1_{h_2}) + \alpha_y \beta^1_y) \\ &\quad - (\mu + \sigma + \eta)\pi^0_{h_2},\end{aligned}$$

and

$$\frac{d\pi^0_y}{dt} = \pi^0_{h_1}\sigma - (\mu + \eta)\pi^0_y - \psi\pi^0_y.$$

Similarly for naive immune z PWIDs we have

$$\frac{d\pi^0_z}{dt} = \sigma\alpha\pi^0_{h_2} - (\mu + \eta)\pi^0_z.$$

Again by using the similar techniques which are used to derive the behaviour of naive PWIDs at each stage of infection over time then we can use a similar way to describe the behaviour of experienced PWIDs at each stage of infection over time. Therefore, the twelve equations that describe the behaviour of all PWIDs over time are given by

$$\frac{d\pi^0_x}{dt} = \mu - (\mu + \eta)\pi^0_x - f_0\pi^0_x + \psi\pi^0_y, \tag{4.2.5}$$

$$\frac{d\pi^0_{x_1}}{dt} = \sigma(1-\alpha)\pi^0_{h_2} - (\mu + \eta)\pi^0_{x_1} - f_0\pi^0_{x_1}, \tag{4.2.6}$$

$$\frac{d\pi^0_{h_1}}{dt} = (1-\delta)f_0\big(\pi^0 - \Sigma_k \pi^0_k\big) - (\mu + \sigma + \eta)\pi^0_{h_1}, \tag{4.2.7}$$

$$\frac{d\pi^0_{h_2}}{dt} = \delta f_0\big(\pi^0 - \Sigma_k \pi^0_k\big) - (\mu + \sigma + \eta)\pi^0_{h_2}, \tag{4.2.8}$$

$$\frac{d\pi^0_y}{dt} = \sigma\pi^0_{h_1} - (\mu + \eta)\pi^0_y - \psi\pi^0_y, \tag{4.2.9}$$

$$\frac{d\pi^0_z}{dt} = \sigma\alpha\pi^0_{h_2} - (\mu + \eta)\pi^0_z, \tag{4.2.10}$$

$$\frac{d\pi^1_x}{dt} = \eta\pi^0_x - \mu\pi^1_x - f_1\pi^1_x + \psi\pi^1_y, \tag{4.2.11}$$

$$\frac{d\pi^1_{x_1}}{dt} = \eta\pi^0_{x_1} + \sigma(1-\alpha)\pi^1_{h_2} - \mu\pi^1_{x_1} - f_1\pi^1_{x_1}, \tag{4.2.12}$$

$$\frac{d\pi^1_{h_1}}{dt} = \eta\pi^0_{h_1} + (1-\delta)f_1\big(\pi^1 - \Sigma_k \pi^1_k\big) - (\mu + \sigma)\pi^1_{h_1}, \tag{4.2.13}$$

$$\frac{d\pi^1_{h_2}}{dt} = \eta\pi^0_{h_2} + \delta f_1\big(\pi^1 - \Sigma_k \pi^1_k\big) - (\mu + \sigma)\pi^1_{h_2}, \tag{4.2.14}$$

$$\frac{d\pi^1_y}{dt} = \eta\pi^0_y + \sigma\pi^1_{h_1} - \mu\pi^1_y - \psi\pi^1_y, \tag{4.2.15}$$

$$\frac{d\pi^1_z}{dt} = \eta\pi^0_z + \sigma\alpha\pi^1_{h_2} - \mu\pi^1_z, \tag{4.2.16}$$

where $\pi_j^i \geq 0$, $\Sigma_k \pi_k^0 + \Sigma_k \pi_k^1 = 1$ $(k = x, x_1, h_1, h_2, y, z)$ and f_0, f_1 are given by

$$f_i = \lambda_i s_{i0}(1-\phi)(\alpha_h(\beta_{h_1}^0 + \beta_{h_2}^0) + \alpha_y \beta_y^0) + \lambda_i s_{i1}(1-\phi)(\alpha_h(\beta_{h_1}^1 + \beta_{h_2}^1) + \alpha_y \beta_y^1).$$

Equations (4.2.5)-(4.2.10) describe how the behaviour of naive PWIDs at each stage of HCV infection changes over time while equations (4.2.11)-(4.2.16) describe how the behaviour of experienced PWIDs at each infectious stage changes over time.

Needles and syringes

The critical step for this model is the derivation of equations for the change in the fraction of infectious needles and syringes. These particular equations describe the change in the fraction of infectious needles in each category. To fully define the models we need to define m_0 as the number of naive syringes and needles circulating amongst PWIDs, that is the number of needles and syringes that were either last used by a naive PWID or are the last of a sequence of non-used needles or syringes, the first member of which was exchanged for a needle or syringe last used by a naive PWID. This situation implies that this is the number of naive syringes and needles in circulation amongst the number of naive PWIDs in the modelled population. Similarly the model defines m_1 to be the number of experienced needles and syringes in circulation (Corson (2011) and Corson et al. (2013)). We therefore define $\Lambda_{jk} = \frac{\lambda_j s_{jk} n_j}{m_k}, j, k = 0, 1$ as the rate which any PWID in group j injects using a syringe and needle previously used by a group k PWID.

Now as in the first model we have two assumptions. The first (Assumption 1) corresponds to the pessimistic needle assumptions in Lewis and Greenhalgh (2001a) where state h_1 infectious needles are regarded as more infectious than state h_2 infectious needles. So needles only move up the spectrum: uninfectious, state y infectious, state h_2 infectious, then state h_1 infectious. Under Assumption 1

$m_0\beta^0_{h_1}(t+\triangle t)$, the number of naive acute h_1 infected needles at time $t+\triangle t$

$=$ 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 PWIDs in $[t, t+\triangle t)$)

$+$ the number of experienced needles and syringes at time t used by a naive acute h_1 infected PWID in $[t, t+\triangle t)$

$-$ the number of naive acute h_1 infected needles and syringes cleaned then used by a naive non acute h_1 PWID in $[t, t+\triangle t)$

$-$ the number of naive acute h_1 needles and syringes used by experienced PWIDs in $[t, t+\triangle t)$

$+$ (the number of experienced acute h_1 infected needles and syringes at time t) $\times$ (the fraction used without cleaning by naive non acute h_1 PWIDs in $[t, t+\triangle t)$)

$-$ the number of naive acute h_1 needles and syringes exchanged in $[t, t+\triangle t)$.

$$\begin{aligned} m_0\beta^0_{h_1}(t+\triangle t) &= m_0\beta^0_{h_1}(t) + \Lambda_{00}\frac{\pi^0_{h_1}}{\pi^0}m_0(1-\beta^0_{h_1})\triangle t + \Lambda_{01}\frac{\pi^0_{h_1}}{\pi^0}m_1\triangle t \\ &- \phi\Lambda_{00}\left(\frac{\pi^0-\pi^0_{h_1}}{\pi^0}\right)\beta^0_{h_1}m_0\triangle t \\ &- \Lambda_{10}m_0\beta^0_{h_1}\triangle t + \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}}{\pi^0}\right)m_1\beta^1_{h_1}(1-\phi)\triangle t \\ &- m_0\beta^0_{h_1}\tau\triangle t + o(\triangle t). \end{aligned}$$

Subtracting $m_0\beta^0_{h_1}(t)$ from both sides, dividing by $\triangle t$ then letting $\triangle t \to 0$ gives

$$\begin{aligned} m_0\frac{d\beta^0_{h_1}}{dt} &= \Lambda_{00}\frac{\pi^0_{h_1}}{\pi^0}m_0(1-\beta^0_{h_1}) + \Lambda_{01}\frac{\pi^0_{h_1}}{\pi^0}m_1 \\ &- \phi\Lambda_{00}\left(\frac{\pi^0-\pi^0_{h_1}}{\pi^0}\right)\beta^0_{h_1}m_0 \\ &- \Lambda_{10}m_0\beta^0_{h_1} + \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}}{\pi^0}\right)m_1\beta^1_{h_1}(1-\phi) \\ &- m_0\beta^0_{h_1}\tau. \end{aligned} \tag{4.2.17}$$

Similarly

$$\begin{aligned} m_0\beta^0_{h_2}(t+\triangle t) &= m_0\beta^0_{h_2}(t) + \Lambda_{00}\frac{\pi^0_{h_2}}{\pi^0}m_0(1-\beta^0_{h_1}-\beta^0_{h_2})\triangle t \\ &+ \Lambda_{01}\frac{\pi^0_{h_2}}{\pi^0}m_1[(1-\beta^1_{h_1})+\phi\beta^1_{h_1}]\triangle t \\ &+ \phi\Lambda_{00}\beta^0_{h_1}\frac{\pi^0_{h_2}}{\pi_0}m_0\triangle t - \Lambda_{00}\frac{\pi^0_{h_1}}{\pi_0}\beta^0_{h_2}m_0\triangle t \\ &- \Lambda_{10}m_0\beta^0_{h_2}\triangle t \\ &- \phi\Lambda_{00}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)\beta^0_{h_2}m_0\triangle t \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)m_1\beta^1_{h_2}(1-\phi)\triangle t \\ &- m_0\beta^0_{h_2}\tau\triangle t + o(\triangle t). \end{aligned}$$

Subtracting $m_0\beta^0_{h_2}(t)$ from both sides, dividing by $\triangle t$ then letting $\triangle t \to 0$ gives

$$\begin{aligned} m_0\frac{d\beta^0_{h_2}}{dt} &= \Lambda_{00}\frac{\pi^0_{h_2}}{\pi^0}m_0(1-\beta^0_{h_1}-\beta^0_{h_2}) \\ &+ \Lambda_{01}\frac{\pi^0_{h_2}}{\pi^0}m_1[(1-\beta^1_{h_1})+\phi\beta^1_{h_1}] \\ &+ \phi\Lambda_{00}\beta^0_{h_1}\frac{\pi^0_{h_2}}{\pi^0}m_0 - \Lambda_{00}\frac{\pi^0_{h_1}}{\pi^0}\beta^0_{h_2}m_0 \\ &- \Lambda_{10}m_0\beta^0_{h_2} \\ &- \phi\Lambda_{00}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)\beta^0_{h_2}m_0 \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)m_1\beta^1_{h_2}(1-\phi) \\ &- m_0\beta^0_{h_2}\tau. \end{aligned} \tag{4.2.18}$$

Under Assumption 2 the equations for naive state β_{h_1} needles are

$$\begin{aligned} m_0\beta^0_{h_1}(t+\triangle t) = m_0\beta^0_{h_1}(t) &+ \Lambda_{00}\frac{\pi^0_{h_1}}{\pi^0}m_0(1-\beta^0_{h_1})\triangle t + \Lambda_{01}\frac{\pi^0_{h_1}}{\pi^0}m_1\triangle t \\ &- \Lambda_{00}\frac{\pi^0_{h_2}}{\pi^0}(1-\phi)m_0\beta^0_{h_1}\triangle t \\ &- \phi\Lambda_{00}\left(\frac{\pi^0-\pi^0_{h_1}}{\pi^0}\right)\beta^0_{h_1}m_0\triangle t - \Lambda_{10}m_0\beta^0_{h_1}\triangle t \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)m_1\beta^1_{h_1}(1-\phi)\triangle t \\ &- m_0\beta^0_{h_1}\tau\triangle t + o(\triangle t). \end{aligned}$$

Subtracting $m_0\beta^0_{h_1}(t)$ from both sides, dividing by $\triangle t$ then letting $\triangle t \to 0$ gives

$$\begin{aligned} m_0\frac{d\beta^0_{h_1}}{dt} &= \Lambda_{00}\frac{\pi^0_{h_1}}{\pi^0}m_0(1-\beta^0_{h_1}) + \Lambda_{01}\frac{\pi^0_{h_1}}{\pi^0}m_1 \\ &- \Lambda_{00}\frac{\pi^0_{h_2}}{\pi^0}(1-\phi)m_0\beta^0_{h_1} \\ &- \phi\Lambda_{00}\left(\frac{\pi^0-\pi^0_{h_1}}{\pi^0}\right)\beta^0_{h_1}m_0 - \Lambda_{10}m_0\beta^0_{h_1} \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)m_1\beta^1_{h_1}(1-\phi) \\ &- m_0\beta^0_{h_1}\tau. \end{aligned} \tag{4.2.19}$$

Similarly

$$\begin{aligned} m_0\beta^0_{h_2}(t+\triangle t) &= m_0\beta^0_{h_2}(t) + \Lambda_{00}\frac{\pi^0_{h_2}}{\pi^0}m_0(1-\beta^0_{h_2})\triangle t \\ &- \Lambda_{00}\frac{\pi^0_{h_1}}{\pi^0}(1-\phi)m_0\beta^0_{h_2}\triangle t \\ &+ \Lambda_{01}\frac{\pi^0_{h_2}}{\pi^0}m_1\triangle t \\ &- \phi\Lambda_{00}\beta^0_{h_2}\left(\frac{\pi^0-\pi^0_{h_2}}{\pi^0}\right)m_0\triangle t \\ &- \Lambda_{10}m_0\beta^0_{h_2}\triangle t \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)\beta^1_{h_2}m_1(1-\phi)\triangle t \\ &- m_0\beta^0_{h_2}\tau\triangle t + o(\triangle t). \end{aligned}$$

Subtracting $m_0\beta^0_{h_2}(t)$ from both sides, dividing by $\triangle t$ then letting $\triangle t \to 0$ gives

$$\begin{aligned} m_0\frac{d\beta^0_{h_2}}{dt} &= \Lambda_{00}\frac{\pi^0_{h_2}}{\pi^0}m_0(1-\beta^0_{h_2}) \\ &- \Lambda_{00}\frac{\pi^0_{h_1}}{\pi^0}\beta^0_{h_2}(1-\phi) \\ &+ \Lambda_{01}\frac{\pi^0_{h_2}}{\pi^0}m_1 \\ &- \phi\Lambda_{00}\beta^0_{h_2}\left(\frac{\pi^0-\pi^0_{h_2}}{\pi^0}\right)m_0 \\ &- \Lambda_{10}m_0\beta^0_{h_2} \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi^0_{h_1}-\pi^0_{h_2}}{\pi^0}\right)m_1\beta^1_{h_2}(1-\phi) \\ &- m_0\beta^0_{h_2}\tau. \end{aligned} \tag{4.2.20}$$

Now for both Assumptions 1 and 2 in stage chronic y we have that

$$\begin{aligned} m_0\beta_y^0(t+\triangle t) = m_0\beta_y^0(t) &+ \Lambda_{00}\frac{\pi_y^0}{\pi^0}m_0(1-\beta_{h_1}^0-\beta_{h_2}^0-\beta_y^0)\triangle t \\ &+ \Lambda_{01}\frac{\pi_y^0}{\pi^0}m_1[(1-\beta_{h_1}^1-\beta_{h_2}^1)+\phi(\beta_{h_1}^1+\beta_{h_2}^1)]\triangle t \\ &+ \phi\Lambda_{00}\frac{\pi_y^0}{\pi^0}(\beta_{h_1}^0+\beta_{h_2}^0)m_0\triangle t \end{aligned} \tag{4.2.21}$$

$$\begin{aligned} &- \Lambda_{00}m_0\beta_y^0\left(\frac{\pi_{h_1}^0+\pi_{h_2}^0}{\pi^0}\right)\triangle t \\ &- \Lambda_{10}m_0\beta_y^0\triangle t \\ &- \phi\Lambda_{00}\beta_y^0\left(\frac{\pi^0-(\pi_{h_1}^0+\pi_{h_2}^0+\pi_y^0)}{\pi^0}\right)m_0\triangle t \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi_{h_1}^0-\pi_{h_2}^0-\pi_y^0}{\pi^0}\right)m_1\beta_y^1(1-\phi)\triangle t \\ &- m_0\beta_y^0\tau\triangle t + o(\triangle t). \end{aligned} \tag{4.2.22}$$

Subtracting $m_0\beta_y^0(t)$ from both sides, dividing by $\triangle t$ then letting $\triangle t \to 0$ gives

$$\begin{aligned} m_0\frac{d\beta_y^0}{dt} &= \Lambda_{00}\frac{\pi_y^0}{\pi^0}m_0(1-\beta_{h_1}^0-\beta_{h_2}^0-\beta_y^0) \\ &+ \Lambda_{01}\frac{\pi_y^0}{\pi^0}m_1[(1-\beta_{h_1}^1-\beta_{h_2}^1)+\phi(\beta_{h_1}^1+\beta_{h_2}^1)] \\ &+ \phi\Lambda_{00}\frac{\pi_y^0}{\pi^0}(\beta_{h_1}^0+\beta_{h_2}^0)m_0 \\ &- \Lambda_{00}m_0\beta_y^0\left(\frac{\pi_{h_1}^0+\pi_{h_2}^0}{\pi^0}\right) \\ &- \Lambda_{10}m_0\beta_y^0 \\ &- \phi\Lambda_{00}\beta_y^0\left(\frac{\pi^0-(\pi_{h_1}^0+\pi_{h_2}^0+\pi_y^0)}{\pi^0}\right)m_0 \\ &+ \Lambda_{01}\left(\frac{\pi^0-\pi_{h_1}^0-\pi_{h_2}^0-\pi_y^0}{\pi^0}\right)m_1\beta_y^1(1-\phi) \\ &- m_0\beta_y^0\tau. \end{aligned} \tag{4.2.23}$$

Similarly for the experienced stage, we have that for Assumption 1

$$\begin{aligned} m_1 \frac{d\beta^1_{h_1}}{dt} &= \Lambda_{11} \frac{\pi^1_{h_1}}{\pi^1} m_1 (1 - \beta^1_{h_1}) + \Lambda_{10} \frac{\pi^1_{h_1}}{\pi^1} m_0 \\ &- \phi \Lambda_{11} \left(\frac{\pi^1 - \pi^1_{h_1}}{\pi^1} \right) \beta^1_{h_1} m_1 \\ &- \Lambda_{01} m_1 \beta^1_{h_1} + \Lambda_{10} \left(\frac{\pi^1 - \pi^1_{h_1}}{\pi^1} \right) m_0 \beta^0_{h_1} (1 - \phi) \\ &- m_1 \beta^1_{h_1} \tau. \end{aligned} \tag{4.2.24}$$

For acute h_2 we have

$$\begin{aligned} m_1 \frac{d\beta^1_{h_2}}{dt} &= \Lambda_{11} \frac{\pi^1_{h_2}}{\pi^1} m_1 (1 - \beta^1_{h_1} - \beta^1_{h_2}) \\ &+ \Lambda_{10} \frac{\pi^1_{h_2}}{\pi^1} m_0 \left[(1 - \beta^0_{h_1}) + \phi \beta^0_{h_1} \right] \\ &+ \phi \Lambda_{11} \beta^1_{h_1} \frac{\pi^1_{h_2}}{\pi^1} m_1 - \Lambda_{11} \frac{\pi^1_{h_1}}{\pi^1} \beta^1_{h_2} m_1 \\ &- \Lambda_{01} m_1 \beta^1_{h_2} \\ &- \phi \Lambda_{11} \left(\frac{\pi^1 - \pi^1_{h_1} - \pi^1_{h_2}}{\pi^1} \right) \beta^1_{h_2} m_1 \\ &+ \Lambda_{10} \left(\frac{\pi^1 - \pi^1_{h_1} - \pi^1_{h_2}}{\pi^1} \right) m_1 \beta^0_{h_2} (1 - \phi) \\ &- m_1 \beta^1_{h_2} \tau. \end{aligned} \tag{4.2.25}$$

Under Assumption 2 we have

$$\begin{aligned} m_1 \frac{d\beta^1_{h_1}}{dt} &= \Lambda_{11} \frac{\pi^1_{h_1}}{\pi^1} m_1 (1 - \beta^1_{h_1}) + \Lambda_{10} \frac{\pi^1_{h_1}}{\pi^1} m_0 \\ &- \phi \Lambda_{11} \left(\frac{\pi^1 - \pi^1_{h_1}}{\pi^1} \right) \beta^1_{h_1} m_1 - \Lambda_{01} m_1 \beta^1_{h_1} \\ &- \Lambda_{11} \frac{\pi^1_{h_2}}{\pi^1} (1 - \phi) m_1 \beta^1_{h_1} \\ &+ \Lambda_{10} \left(\frac{\pi^1 - \pi^1_{h_1} - \pi^1_{h_2}}{\pi^1} \right) m_0 \beta^0_{h_1} (1 - \phi) \\ &- m_1 \beta^1_{h_1} \tau. \end{aligned} \tag{4.2.26}$$

$$
\begin{aligned}
m_1\frac{d\beta^1_{h_2}}{dt} &= \Lambda_{11}\frac{\pi^1_{h_2}}{\pi^1}m_1(1-\beta^1_{h_2}) \\
&+ \Lambda_{10}\frac{\pi^1_{h_2}}{\pi^1}m_0 - \Lambda_{11}\frac{\pi^1_{h_1}}{\pi^1}\beta^1_{h_2}(1-\phi) \\
&- \phi\Lambda_{11}\beta^1_{h_2}\left(\frac{\pi^1-\pi^1_{h_2}}{\pi^1}\right)m_1 \\
&- \Lambda_{01}m_1\beta^1_{h_2} \\
&+ \Lambda_{10}\left(\frac{\pi^1-\pi^1_{h_1}-\pi^1_{h_2}}{\pi^1}\right)m_0\beta^0_{h_2}(1-\phi) \\
&- m_1\beta^1_{h_2}\tau.
\end{aligned} \tag{4.2.27}
$$

Now for both assumptions we have

$$
\begin{aligned}
m_1\frac{d\beta^1_y}{dt} &= \Lambda_{11}\frac{\pi^1_y}{\pi^1}m_1(1-\beta^1_{h_1}-\beta^1_{h_2}-\beta^1_y) \\
&+ \Lambda_{10}\frac{\pi^1_y}{\pi^1}m_0[(1-\beta^0_{h_1}-\beta^0_{h_2})+\phi(\beta^0_{h_1}+\beta^0_{h_2})] \\
&+ \phi\Lambda_{11}\frac{\pi^1_y}{\pi^1}(\beta^1_{h_1}+\beta^1_{h_2})m_1 \\
&- \Lambda_{11}m_1\beta^1_y\left(\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\right) \\
&- \Lambda_{01}m_1\beta^1_y \\
&- \phi\Lambda_{11}\beta^1_y\left(\frac{\pi^1-(\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y)}{\pi^1}\right)m_1 \\
&+ \Lambda_{10}\left(\frac{\pi^1-\pi^1_{h_1}-\pi^1_{h_2}-\pi^1_y}{\pi^1}\right)m_0\beta^0_y(1-\phi) \\
&- m_1\beta^1_y\tau.
\end{aligned} \tag{4.2.28}
$$

The governing equations for the PWID and needle time since first injection model are given by equations (4.2.5)-(4.2.28). This model contains 18 governing equations for Assumption 1 and 18 governing equations for Assumption 2 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 a PWID only model. The approximation argument that was used in the local stability analysis of the endemic equilibrium of the simple model (Theorem 2.4.19) shows that it is possible to have an approximately valid PWID only model which has the same basic reproduction number and equilibrium values as the full model. Hence the system of equations

which govern the behaviour of the model is given by

$$\frac{d\pi_x^0}{dt} = \mu - (\mu+\eta)\pi_x^0 - \tilde{f}_0\pi_x^0 + \psi\pi_y^0, \tag{4.2.29}$$

$$\frac{d\pi_{x_1}^0}{dt} = \sigma(1-\alpha)\pi_{h_2}^0 - (\mu+\eta)\pi_{x_1}^0 - \tilde{f}_0\pi_{x_1}^0, \tag{4.2.30}$$

$$\frac{d\pi_{h_1}^0}{dt} = (1-\delta)\tilde{f}_0\big(\pi^0 - \Sigma_k\pi_k^0\big) - (\mu+\sigma+\eta)\pi_{h_1}^0, \tag{4.2.31}$$

$$\frac{d\pi_{h_2}^0}{dt} = \delta\tilde{f}_0\big(\pi^0 - \Sigma_k\pi_k^0\big) - (\mu+\sigma+\eta)\pi_{h_2}^0, \tag{4.2.32}$$

$$\frac{d\pi_y^0}{dt} = \sigma\pi_{h_1}^0 - (\mu+\eta)\pi_y^0 - \psi\pi_y^0, \tag{4.2.33}$$

$$\frac{d\pi_z^0}{dt} = \sigma\alpha\pi_{h_2}^0 - (\mu+\eta)\pi_z^0, \tag{4.2.34}$$

$$\frac{d\pi_x^1}{dt} = \eta\pi_x^0 - \mu\pi_x^1 - \tilde{f}_1\pi_x^1 + \psi\pi_y^1, \tag{4.2.35}$$

$$\frac{d\pi_{x_1}^1}{dt} = \eta\pi_{x_1}^0 + \sigma(1-\alpha)\pi_{h_2}^1 - \mu\pi_{x_1}^1 - \tilde{f}_1\pi_{x_1}^1, \tag{4.2.36}$$

$$\frac{d\pi_{h_1}^1}{dt} = \eta\pi_{h_1}^0 + (1-\delta)\tilde{f}_1\big(\pi^1 - \Sigma_k\pi_k^1\big) - (\mu+\sigma)\pi_{h_1}^1, \tag{4.2.37}$$

$$\frac{d\pi_{h_2}^1}{dt} = \eta\pi_{h_2}^0 + \delta\tilde{f}_1\big(\pi^1 - \Sigma_k\pi_k^1\big) - (\mu+\sigma)\pi_{h_2}^1, \tag{4.2.38}$$

$$\frac{d\pi_y^1}{dt} = \eta\pi_y^0 + \sigma\pi_{h_1}^1 - \mu\pi_y^1 - \psi\pi_y^1, \tag{4.2.39}$$

$$\frac{d\pi_z^1}{dt} = \eta\pi_z^0 + \sigma\alpha\pi_{h_2}^1 - \mu\pi_z^1, \tag{4.2.40}$$

where $\pi_j^i \geq 0$, $\Sigma_j\pi_j^0 + \Sigma_j\pi_j^1 = 1$ $(j = x, x_1, h_1, h_2, y, z)$ and the summation signs over k are taken over $k = h_1, h_2, y, z$ and $\tilde{f}_0, \tilde{f}_1$ are given by

$$\begin{aligned}\tilde{f}_i &= \lambda_i s_{i0}(1-\phi)\big((\alpha_h-\alpha_y)(\overline{\beta}_{h_1}^0 + \overline{\beta}_{h_2}^0) + \alpha_y(\overline{\beta}_{h_1}^0 + \overline{\beta}_{h_2}^0 + \overline{\beta}_y^0)\big)\\ &+ \lambda_i s_{i1}(1-\phi)\big((\alpha_h-\alpha_y)(\overline{\beta}_{h_1}^1 + \overline{\beta}_{h_2}^1) + \alpha_y(\overline{\beta}_{h_1}^1 + \overline{\beta}_{h_2}^1 + \overline{\beta}_y^1)\big),\end{aligned} \tag{4.2.41}$$

such that

$$\overline{\beta}_{h_1}^0 + \overline{\beta}_{h_2}^0 = \frac{B^0}{A^0} \tag{4.2.42}$$

where

$$\begin{aligned} B^0 &= \Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)+\Lambda_{01}\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0} \\ &+ \Lambda_{10}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right) \\ &+ \Lambda_{10}\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)\left(1-\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}\right)+\Lambda_{10}\Lambda_{01}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0} \\ &+ \Lambda_{10}\Lambda_{01}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)\left(1-\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}\right) \end{aligned}$$

and

$$\begin{aligned} A^0 &= \left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right) \\ &+ \Lambda_{01}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right) \\ &+ \Lambda_{10}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)to \end{aligned}$$

$$+\Lambda_{10}\Lambda_{01}\left[1-(1-\phi)^2\left(1-\tfrac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}\right)\left(1-\tfrac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\right)\right].$$

$$\overline{\beta}^0_{h_1}+\overline{\beta}^0_{h_2}+\overline{\beta}^0_{y}=\frac{D^0}{C^0}. \tag{4.2.43}$$

Here

$$\begin{aligned} D^0 &= \Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_{y}}{\pi^0}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_{y}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right) \\ &+ \Lambda_{01}\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_{y}}{\pi^0} \\ &+ \Lambda_{10}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_{y}}{\pi^0}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_{y}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right) \\ &+ \Lambda_{10}\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_{y}}{\pi^1}(1-\phi)\left(1-\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_{y}}{\pi^0}\right)+\Lambda_{10}\Lambda_{01}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_{y}}{\pi^0} \\ &+ \Lambda_{10}\Lambda_{01}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_{y}}{\pi^1}(1-\phi)\left(1-\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_{y}}{\pi^0}\right) \end{aligned}$$

and

$$\begin{aligned}
C^0 &= \left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
&\quad\times\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)\\
&+ \Lambda_{01}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
&+ \Lambda_{10}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)\\
&+ \Lambda_{10}\Lambda_{01}\left[1-(1-\phi)^2\left(1-\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}\right)\left(1-\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\right)\right].
\end{aligned}$$

Moreover

$$\overline{\beta}^1_{h_1}+\overline{\beta}^1_{h_2}=\frac{B^1}{A^1} \tag{4.2.44}$$

where

$$\begin{aligned}
B^1 &= \Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)+\Lambda_{10}\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\\
&+ \Lambda_{01}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^1}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
&+ \Lambda_{01}\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}(1-\phi)\left(1-\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\right)+\Lambda_{01}\Lambda_{10}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\\
&+ \Lambda_{01}\Lambda_{10}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}(1-\phi)\left(1-\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\right)
\end{aligned}$$

and

$$\begin{aligned}
A^1 &= \left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
&+ \Lambda_{10}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)\\
&+ \Lambda_{01}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
&+ \Lambda_{01}\Lambda_{10}\left[1-(1-\phi)^2\left(1-\frac{\pi^1_{h_1}+\pi^1_{h_2}}{\pi^1}\right)\left(1-\frac{\pi^0_{h_1}+\pi^0_{h_2}}{\pi^0}\right)\right].
\end{aligned}$$

Similarly

$$\overline{\beta}^1_{h_1}+\overline{\beta}^1_{h_2}+\overline{\beta}^1_y=\frac{D^1}{C^1}. \tag{4.2.45}$$

Here

$$
\begin{aligned}
D^1 = {} & \Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
& +\Lambda_{10}\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\\
& +\Lambda_{01}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
& +\Lambda_{01}\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)\left(1-\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\right)+\Lambda_{01}\Lambda_{10}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\\
& +\Lambda_{01}\Lambda_{10}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)\left(1-\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\right)
\end{aligned}
$$

and

$$
\begin{aligned}
C^1 = {} & \left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)\\
& \times\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
& +\Lambda_{10}\left(\Lambda_{11}\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}(1-\phi)+\phi\Lambda_{11}+\tau\right)\\
& +\Lambda_{01}\left(\Lambda_{00}\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}(1-\phi)+\phi\Lambda_{00}+\tau\right)\\
& +\Lambda_{01}\Lambda_{10}\left[1-(1-\phi)^2\left(1-\frac{\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y}{\pi^1}\right)\left(1-\frac{\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y}{\pi^0}\right)\right].
\end{aligned}
$$

We note that this PWID only model is completely different than the analysis of Corson (2011) and Corson et al. (2013). In that case there is a PWID only model but it is much simpler. The calculations behind deriving these equations are straightforward but complicated. We give the explanation of the equation (4.2.42) in detail. The other equations (4.2.43)-(4.2.45) are explained similarly. For Assumption 1 we add (4.2.17) to (4.2.18) to give an equation similar to (4.2.17) for $m_0\frac{d\beta^0_h}{dt}$ where $\beta^0_h=\beta^0_{h_1}+\beta^0_{h_2}$. We then add (4.2.24) to (4.2.25) to get a similar equation to (4.2.24) for $m_1\frac{d\beta^1_h}{dt}$ where $\beta^1_h=\beta^1_{h_1}+\beta^1_{h_2}$. For Assumption 2 exactly the same equations are got by adding equations (4.2.19) and (4.2.20) and (4.2.26) to (4.2.27) we then set the time derivatives

$$\frac{d\beta^0_h}{dt}=\frac{d\beta^1_h}{dt}=0$$

and solve for the equilibrium values of these equations to get (4.2.42). We note that at equilibrium the total number of naive PWIDs who inject with syringes last used

by experienced PWIDs is equal to the total number of experienced PWIDs who inject with syringes last used by naive PWIDs and we assume that this equilibrium has been reached (Corson (2011) and Corson et al. (2013)). This implies that

$$\lambda_0 n_0 s_{01} = \lambda_1 n_1 s_{10} \tag{4.2.46}$$

or equivalently

$$\Lambda_{01} m_1 = \Lambda_{10} m_0$$

which was used in the derivation of (4.2.42).

The model given by (4.2.5)-(4.2.28) is approximately equivalent to the PWID only model given by the equations (4.2.29)-(4.2.45). In deriving this approximately equivalent model given by equations (4.2.29)-(4.2.45) we approximated the dynamic relationship between the PWID and needle stages by observing that a PWID injects on a time scale that is of the order of days whereas the epidemiological and demographic changes are much slower and measured in years. A similar approximation was model in our analysis of the local stability of the endemic equilibrium from the simple model in Chapter 2.

4.3 The basic reproduction number R_0

R_0 is also defined by a dimensionless number and not time-dependent, and thus is also referred to as the basic reproduction (or reproductive) ratio. It can be defined as the ratio of rates or as the secondary cases per infected case.

For notational purposes, each infected individual will be defined by the h-state at the time of infection, versus the current h-state. An individual has h-state j means the individual had h-state j when they were infected. This is also called the "state at birth", since the individual is created, or "born", from an infectious point of view. k_{ij} is defined as the expected number of new infections that have h-state i caused by one individual having h-state j, over the time-period of transmissibility (Diekmann and Heesterbeek (2000)).

Therefore, our derivation of R_0 is based on the derivation in Corson (2011) and Corson et al. (2013) the difference being that there is an additional treatment

rate ψ but the analysis is very different and much more complicated because of the different needle equations. Therefore, we have had to adapt our model from that of Corson (2011) and Corson et al. (2013) because of the different needle equations then we derive our basic reproduction number (R_0). Hence, this method uses the projected number of secondary cases that develops from every primary case found within a given 'virgin' population (Corson (2011), Corson et al. (2013) and Diekmann and Heesterbeek (2000)). For this particular case, 'virgin' population refers to the population at the DFE level when the initial infectious case appears. This number plays a crucial role when it comes to epidemiological models. In these cases the disease usually dies out if $R_0 < 1$ and spreads if $R_0 > 1$. To best derive this basic reproduction number, the modified model to be applied considers two particular cases:

1. The infection chain starts with a single naive PWID.

2. The infection chain starts with a single experienced PWID.

An assumption made for this phenomenon focuses on a scenario where the population has reached the DFE. In this situation, both the novice and experienced PWID numbers alongside naive and experienced syringe and needle numbers all reach equilibrium values.

In both case 1 or case 2 once he or she catches HCV, this individual will move to the h_1 stage with probability $1 - \delta$ and the h_2 stage with probability δ. In both cases he or she will stay there for an average time $1/(\mu + \sigma + \eta)$. The transition probabilities through the various infected stages are the same as in Corson (2011) and Corson et al. (2013) except for (a) leaving the chronic infected naive class where they stay for time $1/(\mu + \eta + \psi)$ and the probabilities of leaving the population, moving to the chronic infected experienced class or being cured are $\mu/(\mu + \eta + \psi)$, $\eta/(\mu + \eta + \psi)$ and $\psi/(\mu + \eta + \psi)$ respectively and (b) leaving the chronic infected naive class where they stay for time $1/(\mu + \psi)$ and the probabilities of leaving the population or being cured are $\mu/(\mu + \psi)$, $\eta/(\mu + \eta + \psi)$ and $\psi/(\mu + \psi)$ respectively.

We define

$x^0 =$ expected number of naive PWIDs infected by a single needle in infectious state h_1 or h_2 last used by a naive PWID

and

$x^1 =$ expected number of naive PWIDs infected by a single needle in infectious state h_1 or h_2 last used by an experienced PWID.

If we consider a single needle in infectious state h_1 or h_2 last used by a naive PWID the next event to happen is that it is either used by a naive PWID and not cleaned with probability $\Lambda_{00}(1-\phi)/(\Lambda_{00}+\Lambda_{10}+\tau)$, or used by an experienced PWID and not cleaned with probability $\Lambda_{10}(1-\phi)/(\Lambda_{00}+\Lambda_{10}+\tau)$ or either cleaned and used or exchanged with probability $\big((\Lambda_{00}+\Lambda_{10})\phi+\tau)\big)/(\Lambda_{00}+\Lambda_{10}+\tau)$. Hence

$$x^0 = \alpha_h \frac{\Lambda_{00}(1-\phi)}{\Lambda_{00}+\Lambda_{10}+\tau} + \frac{\Lambda_{00}(1-\phi)}{\Lambda_{00}+\Lambda_{10}+\tau}x^0 + \frac{\Lambda_{10}(1-\phi)}{\Lambda_{00}+\Lambda_{10}+\tau}x^1$$

and

$$x^1 = \alpha_h \frac{\Lambda_{01}(1-\phi)}{\Lambda_{11}+\Lambda_{01}+\tau} + \frac{\Lambda_{11}(1-\phi)}{\Lambda_{11}+\Lambda_{01}+\tau}x^1 + \frac{\Lambda_{01}(1-\phi)}{\Lambda_{11}+\Lambda_{01}+\tau}x^0.$$

After some algebraic operations, we deduce that

$$x^0 = \frac{\alpha_h(1-\phi)\big[\Lambda_{00}(\Lambda_{01}+\Lambda_{11}\phi+\tau)+\Lambda_{01}\Lambda_{10}(1-\phi)\big]}{(\Lambda_{00}\phi+\Lambda_{10}+\tau)(\Lambda_{11}\phi+\Lambda_{01}+\tau)-\Lambda_{10}\Lambda_{01}(1-\phi)^2}, \tag{4.3.47}$$

and

$$x^1 = \frac{\alpha_h(1-\phi)\Lambda_{01}(\Lambda_{00}+\Lambda_{10}+\tau)}{(\Lambda_{00}\phi+\Lambda_{10}+\tau)(\Lambda_{11}\phi+\Lambda_{01}+\tau)-\Lambda_{10}\Lambda_{01}(1-\phi)^2}.$$

Also let

$y^0 =$ expected number of experienced PWIDs infected by a single needle in infectious state h_1 or h_2 last used by a naive PWID (state 0),

then we have

$$y^0 = \frac{\alpha_h(1-\phi)\Lambda_{10}(\Lambda_{11}+\Lambda_{01}+\tau)}{(\Lambda_{00}\phi+\Lambda_{10}+\tau)(\Lambda_{11}\phi+\Lambda_{01}+\tau)-\Lambda_{10}\Lambda_{01}(1-\phi)^2}.$$

Similarly we have

$y^1 =$ expected number of experienced PWIDs infected by a single needle in infectious state h_1 or h_2 last used by an experienced PWID (state 0).

$$y^1 = \frac{\alpha_h(1-\phi)\big[\Lambda_{11}(\Lambda_{10}+\Lambda_{00}\phi+\tau)+\Lambda_{01}\Lambda_{10}(1-\phi)\big]}{(\Lambda_{00}\phi+\Lambda_{10}+\tau)(\Lambda_{11}\phi+\Lambda_{01}+\tau)-\Lambda_{10}\Lambda_{01}(1-\phi)^2}.$$

If we similarly define

$\bar{x}^0 =$ expected number of naive PWIDs infected by a single needle in infectious state y last used by a naive PWID (state 0),

$\bar{x}^1 =$ expected number of naive PWIDs infected by a single needle in infectious state y last used by an experienced PWID (state 1),

$\bar{y}^0 =$ expected number of experienced PWIDs infected by a single needle in infectious state y last used by a naive PWID (state 0),

and

$\bar{y}^1 =$ expected number of experienced PWIDs infected by a single needle in infectious state y last used by an experienced PWID (state 0),

then it is clear that $\bar{x}^0 = \frac{\alpha_y}{\alpha_h}x^0$, $\bar{x}^1 = \frac{\alpha_y}{\alpha_h}x^1$, $\bar{y}^0 = \frac{\alpha_y}{\alpha_h}y^0$ and $\bar{y}^1 = \frac{\alpha_y}{\alpha_h}y^1$.

Let k_{ij} denote the total number of secondary cases caused in the group j by an

index case in group i. Then

k_{10} = the expected total number of secondary cases caused in the naive group by a single experienced individual needle infected entering the disease free population at equilibrium

= the expected total number of secondary cases caused in the naive group by a single experienced individual needle infected individual who progresses through the various stages of infection starting at the acute h_2 stage of infection

\+ the expected total number of secondary cases caused in the naive group by a single experienced individual needle infected individual who progresses through the various stages of infection starting at the acute h_1 stage of infection.

Therefore,

$$k_{10} = k_{10_{h_2}} + k_{10_{h_1}}$$

where

$k_{10_{h_2}}$ = leaving the acute h_2 infected naive class where they stay for time $1/(\mu+\sigma)$ with probability δ,

and

$k_{10_{h_1}}$ = leaving the acute h_1 infected naive class where they stay for time $1/(\mu+\sigma)$ with probability $1-\delta$, then they move to the experienced chronic class with probability $\sigma/(\mu+\sigma)$ where they stay for expected time $1/(\mu+\psi)$.

In both cases there are $\lambda_1/(\mu+\sigma)$ expected infected needles from the acute class. In the second case there are also $(1-\delta)(\sigma/(\mu+\sigma))(\lambda_1/(\mu+\psi))$ expected infected needles from the chronic class. In the first case the needle is left in the acute infectious state and the expected number of PWIDs infected is x^1. In the second case the needle is

left in the chronic infectious state and the expected number of naive PWIDs infected is $\frac{\alpha_y}{\alpha_h}x^1$. Hence,

$$k_{10} = \frac{\lambda_1}{\mu+\sigma}\left[1+\frac{\alpha_y\sigma(1-\delta)}{\alpha_h(\mu+\psi)}\right]x^1, \tag{4.3.48}$$

and similarly

$$k_{11} = \frac{\lambda_1}{\mu+\sigma}\left[1+\frac{\alpha_y\sigma(1-\delta)}{\alpha_h(\mu+\psi)}\right]y^1. \tag{4.3.49}$$

Then similarly k_{01} and k_{00} are given by:

$$\begin{aligned} k_{01} = &\frac{\lambda_0 y^0}{\mu+\sigma+\eta}\left[1+\frac{\alpha_y\sigma(1-\delta)}{\alpha_h(\mu+\eta+\psi)}\right] \\ &+\frac{\lambda_1 y^1}{\mu+\sigma+\eta}\left[\frac{\eta}{\mu+\sigma}+\frac{\alpha_y}{\alpha_h}\left(\frac{\sigma\eta(1-\delta)}{(\mu+\psi)(\mu+\eta+\psi)}+\frac{\sigma\eta(1-\delta)}{(\mu+\psi)(\mu+\sigma)}\right)\right]. \end{aligned} \tag{4.3.50}$$

$$\begin{aligned} k_{00} = &\frac{\lambda_0 x^0}{\mu+\sigma+\eta}\left[1+\frac{\alpha_y\sigma(1-\delta)}{\alpha_h(\mu+\eta+\psi)}\right] \\ &+\frac{\lambda_1 x^1}{\mu+\sigma+\eta}\left[\frac{\eta}{\mu+\sigma}+\frac{\alpha_y}{\alpha_h}\left(\frac{\sigma\eta(1-\delta)}{(\mu+\psi)(\mu+\eta+\psi)}+\frac{\sigma\eta(1-\delta)}{(\mu+\psi)(\mu+\sigma)}\right)\right]. \end{aligned} \tag{4.3.51}$$

Equations (4.3.51)-(4.3.49) give us the elements of the matrix which is given by

$$\begin{bmatrix} k_{00} & k_{01} \\ k_{10} & k_{11} \end{bmatrix}. \tag{4.3.52}$$

This is a "next generation matrix" in the sense of Diekman and Heesterbeek (1990) and they define R_0 to be the spectral radius of 4.3.52. As discussed earlier the values of R_0 might be different than the values obtained by Van den Drissche and Watmough's method but we would expect it to have the same threshold value. Also we are following the method of Diekman and Heesterbeek. Hence the spectral radius of 4.3.52 is given by

$$R_0 = \frac{1}{2}(k_{00}+k_{11}) + \frac{1}{2}\sqrt{(k_{00}+k_{11})^2 - 4(k_{00}k_{11}-k_{10}k_{01})}, \tag{4.3.53}$$

with k_{00}, k_{01}, k_{10} and k_{11} are given by (4.3.51), (4.3.50), (4.3.48) and (4.3.49) respectively.

4.4 Analytical results

In this section the focus shifts to the transmission model applied in the modified model to be used. Similar to Section 2.4.1 an equilibrium and stability analysis will be carried out to determine the rationale and validity of the equilibrium solutions developed. These steps aim to verify that when $R_0 \leq 1$ the only non-negative solution to the presented system of equations is a disease free state. Additionally, we aim to prove that when $R_0 > 1$ there is a non-zero endemic equilibrium solution. Through a global analysis one can ascertain that the DFE is globally asymptotically stable if $R_0 \leq 1$.

In this case although the structure of the PWID equations is similar to that of Corson et al. (2013) the structure of the needle equations is very different. Based on the previous analysis carried out, the modified model assumes that the probability of successful syringe and needle cleaning, ϕ, is between zero and one but strictly less than one, so that $0 \leq \phi < 1$ also $0 \leq \delta < 1$. Let $\pi_j^{i*}, j = h_1, h_2, y, z$ denote the equilibrium proportions of naive ($i = 0$) and experienced ($i = 1$) PWIDs. Setting $d/dt = 0$ in equations (4.2.33), (4.2.34), (4.2.39) and (4.2.40) we find that

$$\begin{aligned} \pi_y^{0*} &= \frac{\sigma}{\mu+\eta+\psi}\pi_{h_1}^{0*}, \\ \pi_z^{0*} &= \frac{\sigma\alpha}{\mu+\eta}\pi_{h_2}^{0*}, \\ \pi_y^{1*} &= \frac{\eta\pi_y^{0*}+\sigma\pi_{h_1}^{1*}}{\mu+\psi}, \\ \pi_z^{1*} &= \frac{\eta\pi_z^{0*}+\sigma\alpha\pi_{h_2}^{1*}}{\mu}. \end{aligned} \tag{4.4.54}$$

Now using equations (4.2.31) and (4.2.32), which are the main driving force for disease amongst naive PWIDs, with $d/dt = 0$ we obtain

$$\pi_{h_1}^{0*} = (1-\delta)\left(\frac{\pi^0 - \pi_{h_1}^{0*} - \pi_{h_2}^{0*} - \pi_y^{0*} - \pi_z^{0*}}{\mu+\sigma+\eta}\right)\tilde{f}_0 \tag{4.4.55}$$

and

$$\pi_{h_2}^{0*} = \delta\left(\frac{\pi^0 - \pi_{h_1}^{0*} - \pi_{h_2}^{0*} - \pi_y^{0*} - \pi_z^{0*}}{\mu+\sigma+\eta}\right)\tilde{f}_0 \tag{4.4.56}$$

where

$$\begin{aligned}\tilde{f}_i &= \lambda_i s_{i0}(1-\phi)\big((\alpha_h-\alpha_y)(\overline{\beta}^0_{h_1}+\overline{\beta}^0_{h_2})+\alpha_y(\overline{\beta}^0_{h_1}+\overline{\beta}^0_{h_2}+\overline{\beta}^0_y)\big)\\ &\quad+\lambda_i s_{i1}(1-\phi)\big((\alpha_h-\alpha_y)(\overline{\beta}^1_{h_1}+\overline{\beta}^1_{h_2})+\alpha_y(\overline{\beta}^1_{h_1}+\overline{\beta}^1_{h_2}+\overline{\beta}^1_y)\big).\end{aligned}$$

Adding these together gives

$$\pi^{0*}_h = \left(\frac{\pi^*_0-\pi^{0*}_h-\pi^{0*}_y-\pi^{0*}_z}{\mu+\sigma+\eta}\right)\tilde{f}_0$$

where $\pi^{0*}_h=\pi^{0*}_{h_1}+\pi^{0*}_{h_2}$, now let $K^*_0=\pi^*_0\tilde{f}_0$ then we have

$$\pi^{0*}_h = \frac{K^*_0}{\mu+\sigma+\eta}\left(1-\frac{\pi^{0*}_h}{\pi^*_0}\left(1+\frac{\sigma(1-\delta)}{\mu+\eta+\psi}+\frac{\sigma\alpha\delta}{\mu+\eta}\right)\right). \tag{4.4.57}$$

Solving (4.4.57) for π^{0*}_h and substituting in the equilibrium expression for π^*_0 we obtain

$$\pi^{0*}_h=\frac{\frac{K^*_0}{\mu+\sigma+\eta}}{1+\frac{K^*_0}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\mu}+\frac{\sigma(1-\delta)(\mu+\eta)}{\mu(\mu+\eta+\psi)}+\frac{\sigma\alpha\delta}{\mu}\right)}. \tag{4.4.58}$$

We now use a similar procedure for the equations that make HCV spread amongst experienced PWIDs. We write $\pi^1_h=\pi^1_{h_1}+\pi^1_{h_2}$, so $\pi^{1*}_h=\pi^{1*}_{h_1}+\pi^{1*}_{h_2}$, and note that equations (4.2.37) and (4.2.38) imply that $\pi^{1*}_{h_1}=(1-\delta)\pi^{1*}_h$ and $\pi^{1*}_{h_2}=\delta\pi^{1*}_h$. Considering equations (4.2.37)-(4.2.38) and adding them together with $d/dt=0$ and substituting in the necessary equilibrium expressions (4.4.54) then that gives

$$\begin{aligned}\pi^{1*}_h &= \frac{\eta\pi^{0*}_h}{\mu+\sigma}+\frac{K^*_1}{\mu+\sigma}\left[1-\frac{\pi^{1*}_h}{\pi^*_1}\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}+\frac{\sigma\alpha\delta}{\mu}\right)\right.\\ &\quad\left.-\frac{\pi^{0*}_h}{\pi^*_1}\left(\frac{\eta\sigma(1-\delta)}{(\mu+\psi)(\mu+\psi+\eta)}+\frac{\eta\sigma\alpha\delta}{\mu(\mu+\eta)}\right)\right]\end{aligned} \tag{4.4.59}$$

where $K^*_1=\pi^*_1\tilde{f}_1$. Recall that $\pi^*_0+\pi^*_1=1$, $\pi^*_0=\mu/(\mu+\eta)$ and $\pi^*_1=\eta/(\mu+\eta)$. Substituting (4.4.58) in this expression for π^*_1 we obtain

$$\pi^{1*}_h = \frac{\frac{\eta K^*_0}{(\mu+\sigma)(\mu+\sigma+\eta)}+\frac{K^*_1}{\mu+\sigma}\left[1+\frac{K^*_0}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\eta}+\frac{(\mu+\eta)\sigma(1-\delta)\psi}{\mu(\mu+\psi)(\mu+\eta+\psi)}\right)\right]}{\left[1+\frac{K^*_1(\mu+\eta)}{(\mu+\sigma)\eta}\left(1+\frac{\sigma(1-\delta)}{\mu+\psi}+\frac{\sigma\alpha\delta}{\mu}\right)\right]\left[1+\frac{K^*_0}{\mu+\sigma+\eta}\left(\frac{\mu+\eta}{\eta}+\frac{\sigma(1-\delta)(\mu+\eta)}{\mu(\mu+\eta+\psi)}+\frac{\sigma\alpha\delta}{\mu}\right)\right]}. \tag{4.4.60}$$

If we represent $\boldsymbol{K} = (K_0, K_1)$ then recall that

$$\begin{aligned} K_0^* &= \pi_0^* \tilde{f}_0 \\ &= \pi_0^* \Bigg[\lambda_0 s_{00}(1-\phi)\left(\frac{(\alpha_h - \alpha_y)B^0}{A^0} + \frac{\alpha_y D^0}{C^0}\right) \\ &\qquad + \lambda_1 s_{01}(1-\phi)\left(\frac{(\alpha_h - \alpha_y)B^1}{A^1} + \frac{\alpha_y D^1}{C^1}\right)\Bigg]. \end{aligned}$$

Now note as $A^0, B^0, A^1, B^1, C^0, D^0$ and C^1, D^1 are all functions of π_h^{0*} and π_h^{1*}, hence using (4.2.42)-(4.2.45) along with expressions (4.4.54), (4.4.58) and (4.4.60) they are functions of K_0^* and K_1^*. Moreover B^0, B^1, D^0 and D^1 can be written in the form

$$\overline{M}_{00}(\boldsymbol{K}^*)\boldsymbol{K}_0^* + \overline{M}_{01}(\boldsymbol{K}^*)\boldsymbol{K}_1^*$$

where $\overline{M}_{00}(\boldsymbol{K}^*)$ and $\overline{M}_{01}(\boldsymbol{K}^*)$ are functions of $\boldsymbol{K}^*$.

Applying a similar argument to K_1^* we deduce that

$$\boldsymbol{K}^* = \boldsymbol{M}(\boldsymbol{K}^*)\boldsymbol{K}^*, \tag{4.4.61}$$

where $\boldsymbol{M}(\boldsymbol{K})$ is a strictly positive matrix function. Moreover for $\boldsymbol{K} \geq \boldsymbol{0}, \boldsymbol{K} \neq \boldsymbol{0}$ then $M_{ij}(\boldsymbol{K}) < M_{ij}(\boldsymbol{0})$ $i = 0, 1$, $j = 0, 1$ and $\boldsymbol{M}(\boldsymbol{0})^T$ is the next generation matrix (4.3.52) .

To show that if $\boldsymbol{K}^* \geq 0$, $\boldsymbol{K}^* \neq 0$ then $M_{ij}(\boldsymbol{K}^*) < M_{ij}(\boldsymbol{0}), i = 0, 1, j = 0, 1$ note that using (4.4.57) and (4.4.59)

$$\frac{\pi_h^{0*}(K_0^*, K_1^*)}{\pi_0^*} = \tilde{M}_{00}(\boldsymbol{K}^*)K_0^*$$

and

$$\frac{\pi_h^{1*}(K_0^*, K_1^*)}{\pi_1^*} = \tilde{M}_{10}(\boldsymbol{K}^*)K_0^* + \tilde{M}_{11}(\boldsymbol{K}^*)K_1^*$$

where

(i) if $K_0^* > 0$ then $\tilde{M}_{00}(\boldsymbol{K}^*) < \tilde{M}_{00}(\boldsymbol{0})$,

(ii) if either $K_0^* > 0$ or $K_1^* > 0$ then $\tilde{M}_{1j}(\boldsymbol{K}^*) < \tilde{M}_{1j}(\boldsymbol{0}), j = 0, 1$.

Hence using (4.53) the same is true for

$$\frac{\pi_h^{i*}(K_0^*, K_1^*)}{\pi_i^*} + \frac{\pi_y^{i*}(K_0^*, K_1^*)}{\pi_i^*}, i = 0, 1.$$

Note that

$$\overline{\beta}_h^{0*} = \frac{B^0}{A^0}$$
$$= \frac{(\Lambda_{00}+\Lambda_{10})\frac{\pi_h^{0*}}{\pi_0^*}}{\left(\Lambda_{00}\frac{\pi_h^{0*}}{\pi_0^*}+\phi\Lambda_{00}\frac{(\pi_0^*-\pi_h^{0*})}{\pi_0^*}+\Lambda_{10}+\tau\right)}\frac{1}{(1-\alpha_h)}$$
$$+\frac{\Lambda_{10}\frac{(\pi_0^*-\pi_h^{0*})}{\pi_0^*}(1-\phi)}{\left(\Lambda_{00}\frac{\pi_h^{0*}}{\pi_0^*}+\phi\Lambda_{00}\frac{(\pi_0^*-\pi_h^{0*})}{\pi_0^*}+\Lambda_{10}+\tau\right)}\frac{(\Lambda_{11}+\Lambda_{01})\frac{\pi_h^{1*}}{\pi_1^*}}{\left(\Lambda_{11}\frac{\pi_h^{1*}}{\pi_1^*}+\phi\Lambda_{11}\frac{(\pi_1^*-\pi_h^{1*})}{\pi_1^*}+\Lambda_{01}+\tau\right)}\frac{1}{(1-\alpha_h)} \tag{4.4.62}$$

where

$$\alpha_h = \frac{\Lambda_{10}\Lambda_{01}\left(1-\frac{\pi_h^{0*}}{\pi_0^*}\right)\left(1-\frac{\pi_h^{1*}}{\pi_1^*}\right)(1-\phi)^2}{\left(\Lambda_{00}\frac{\pi_h^{0*}}{\pi_0^*}+\phi\Lambda_{00}\left(1-\frac{\pi_h^{0*}}{\pi_0^*}\right)+\Lambda_{10}+\tau\right)\left(\Lambda_{11}\frac{\pi_h^{1*}}{\pi_1^*}+\phi\Lambda_{11}\left(1-\frac{\pi_h^{1*}}{\pi_1^*}\right)+\Lambda_{01}+\tau\right)} < 1. \tag{4.4.63}$$

Now using (4.4.62) and (4.4.63)

$$\overline{\beta}_h^0 = \frac{(\Lambda_{00}+\Lambda_{10})\tilde{M}_{00}(\boldsymbol{K}^*)K_0^*}{\left(\phi\Lambda_{00}+\Lambda_{00}\frac{\pi_h^0(\boldsymbol{K}^*)}{\pi_0^*}(1-\phi)+\Lambda_{10}+\tau\right)}\frac{1}{(1-\alpha_h(\boldsymbol{K}^*))}$$
$$+\frac{\Lambda_{10}\left(1-\frac{\pi_h^{0*}(\boldsymbol{K}^*)}{\pi_0^*}\right)\left((1-\phi)(\Lambda_{11}+\Lambda_{01})[\tilde{M}_{10}(\boldsymbol{K}^*)K_0^*+\tilde{M}_{11}(\boldsymbol{K}^*)K_1^*]\right)}{\left(\phi\Lambda_{00}+\Lambda_{00}\frac{\pi_h^0(\boldsymbol{K}^*)}{\pi_0^*}(1-\phi)+\Lambda_{10}+\tau\right)\left(\phi\Lambda_{11}+\Lambda_{11}\frac{\pi_h^1(\boldsymbol{K}^*)}{\pi_1^*}(1-\phi)+\Lambda_{01}+\tau\right)}$$
$$\frac{1}{(1-\alpha_h(\boldsymbol{K}^*))} \tag{4.4.64}$$

where $\alpha_h(\boldsymbol{K}^*) =$

$$\frac{\Lambda_{10}\Lambda_{01}\left(1-\frac{\pi_h^0(\boldsymbol{K}^*)}{\pi_0^*}\right)\left(1-\frac{\pi_h^1(\boldsymbol{K}^*)}{\pi_1^*}\right)(1-\phi)^2}{\left(\phi\Lambda_{00}+\Lambda_{00}\frac{\pi_h^0(\boldsymbol{K}^*)}{\pi_0^*}(1-\phi)+\Lambda_{10}+\tau\right)\left(\phi\Lambda_{11}+\Lambda_{11}\frac{\pi_h^1(\boldsymbol{K}^*)}{\pi_1^*}(1-\phi)+\Lambda_{01}+\tau\right)}$$
$$\leq \alpha_h(\boldsymbol{0}) = \frac{\Lambda_{10}\Lambda_{01}(1-\phi)^2}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)}.$$

Equation (4.4.64) expresses

$$\bar{\beta}_h^0 = F_{00}(\boldsymbol{K}^*)K_0^* + F_{01}(\boldsymbol{K}^*)K_1^*$$

where F_{00} and F_{01} are strictly positive functions, $F_{00}(\boldsymbol{K}^*) \leq F_{00}(\boldsymbol{0}), F_{01}(\boldsymbol{K}^*) \leq F_{01}(\boldsymbol{0})$ and if $\boldsymbol{K}^* \geq \boldsymbol{0}$ but $\boldsymbol{K}^* \neq \boldsymbol{0}$ then $F_{00}(\boldsymbol{K}^*) < F_{00}(\boldsymbol{0})$ and $F_{01}(\boldsymbol{K}^*) < F_{01}(\boldsymbol{0})$.

A similar argument using (4.2.43), (4.2.44) and (4.2.45) shows that we can express

$$\begin{aligned}\bar{\beta}_h^1 &= F_{10}(\boldsymbol{K}^*)K_0^* + F_{11}(\boldsymbol{K}^*)K_1^*,\\ \bar{\beta}_h^0 + \bar{\beta}_y^0 &= \overline{F}_{00}(\boldsymbol{K}^*)K_0^* + \overline{F}_{01}(\boldsymbol{K}^*)K_1^*,\\ \bar{\beta}_h^1 + \bar{\beta}_y^1 &= \overline{F}_{10}(\boldsymbol{K}^*)K_0^* + \overline{F}_{11}(\boldsymbol{K}^*)K_1^*,\end{aligned}$$

in a similar format where $F_{10}(\boldsymbol{K}^*), F_{11}(\boldsymbol{K}^*), \overline{F}_{00}(\boldsymbol{K}^*), \overline{F}_{01}(\boldsymbol{K}^*), \overline{F}_{10}(\boldsymbol{K}^*)$ and $\overline{F}_{11}(\boldsymbol{K}^*)$ have the same properties as $F_{00}(\boldsymbol{K}^*)$ and $F_{01}(\boldsymbol{K}^*)$.

Now we have

$$K_0^* = \pi_0^* f_0(\boldsymbol{K}^*), \tag{4.4.65}$$

$$K_1^* = \pi_1^* f_1(\boldsymbol{K}^*), \tag{4.4.66}$$

where for $i = 0, 1$, f_i is given by (4.40). Hence for $\boldsymbol{K}^* > \boldsymbol{0}, \boldsymbol{K}^* \neq \boldsymbol{0}$ $M_{ij}(\boldsymbol{K}^*) < M_{ij}(\boldsymbol{0})$.

To show that $\boldsymbol{M}(\boldsymbol{0})$ is the transpose of the next generation matrix consider $M_{00}(\boldsymbol{0})$ which is the coefficient of K_0^* in the right hand side of the equation (4.4.65) when we set $K_0^* = K_1^* = 0$ in this expression

$$\begin{aligned}M_{00}(\boldsymbol{0}) = A&\left(\alpha_h + \frac{\alpha_y\sigma(1-\delta)}{\mu+\psi+\eta}\right)\frac{1}{\mu+\sigma+\eta}\\ &+ B\left[\frac{\eta}{\mu+\sigma}\left(\alpha_h + \frac{\alpha_y\sigma(1-\delta)}{\mu+\psi}\right)\frac{1}{\mu+\sigma+\eta}\right.\\ &\left.+ \frac{\eta\sigma(1-\delta)\alpha_y}{(\mu+\psi)(\mu+\eta+\psi)(\mu+\sigma+\eta)}\right]\end{aligned}$$

where

$$\begin{aligned}A = &\frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{00}+\Lambda_{10})(\phi\Lambda_{11}+\Lambda_{01}+\tau)}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau) - \Lambda_{01}\Lambda_{10}(1-\phi)^2}\\ &+ \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{00}+\Lambda_{10})\Lambda_{01}(1-\phi)}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau) - \Lambda_{01}\Lambda_{10}(1-\phi)^2}\end{aligned}$$

and

$$\begin{aligned}B = &\frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{11}+\Lambda_{01})\Lambda_{10}(1-\phi)\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau) - \Lambda_{01}\Lambda_{10}(1-\phi)^2}\\ &+ \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{11}+\Lambda_{01})(\phi\Lambda_{00}+\Lambda_{01}+\tau)\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau) - \Lambda_{01}\Lambda_{10}(1-\phi)^2}.\end{aligned}$$

So

$$M_{00}(\boldsymbol{0}) = \frac{A\alpha_h}{\mu+\sigma+\eta}\left[1+\frac{\alpha_y}{\alpha_h}\left(\frac{\sigma(1-\delta)}{(\mu+\eta+\psi)}\right)\right] + \frac{B\alpha_h}{\mu+\sigma+\eta}\left[\frac{\eta}{\mu+\sigma}+\frac{\alpha_y}{\alpha_h}\left(\frac{\sigma\eta(1-\delta)}{(\mu+\psi)(\mu+\eta+\psi)} + \frac{\sigma\eta(1-\delta)}{(\mu+\psi)(\mu+\sigma)}\right)\right]. \quad (4.4.67)$$

Here

$$A = \frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{00}+\Lambda_{10})(\phi\Lambda_{11}+\Lambda_{01}+\tau)}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)-\Lambda_{01}\Lambda_{10}(1-\phi)^2} + \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{00}+\Lambda_{10})\Lambda_{01}(1-\phi)}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)-\Lambda_{01}\Lambda_{10}(1-\phi)^2}.$$

Now

$$s_{00}(\Lambda_{00}+\Lambda_{10}) = s_{00}\left(\frac{\lambda_0 n_0 s_{00}}{m_0}+\frac{\lambda_1 n_1 s_{10}}{m_0}\right) = s_{00}\left(\frac{\lambda_0 n_0 s_{00}}{m_0}+\frac{\lambda_0 n_0 s_{01}}{m_0}\right)$$

as $\lambda_1 n_1 s_{10} = \lambda_0 n_0 s_{01}$

$$= \frac{s_{00}\lambda_0 n_0}{m_0}$$

as $s_{00}+s_{01}=1$

$$= \Lambda_{00}.$$

Similarly

$$s_{01}(\Lambda_{00}+\Lambda_{10}) = \frac{s_{01}\lambda_0 n_0}{m_0} = \frac{s_{10}\lambda_1 n_1}{m_0} = \Lambda_{10}.$$

Hence $\lambda_0 s_{00}(1-\phi)(\Lambda_{00}+\Lambda_{10})(\phi\Lambda_{11}+\Lambda_{01}+\tau)+\lambda_0 s_{01}(1-\phi)^2(\Lambda_{00}+\Lambda_{10})\Lambda_{01}$

$$= \lambda_0(1-\phi)\Lambda_{00}(\phi\Lambda_{11}+\Lambda_{01}+\tau)+\lambda_0\Lambda_{01}\Lambda_{10}(1-\phi)^2.$$

So $A\alpha_h = \lambda_0 x^0$. Now

$$B = \frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{11}+\Lambda_{01})\Lambda_{10}(1-\phi)\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)-\Lambda_{01}\Lambda_{10}(1-\phi)^2} + \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{11}+\Lambda_{01})(\phi\Lambda_{00}+\Lambda_{01}+\tau)\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)-\Lambda_{01}\Lambda_{10}(1-\phi)^2}.$$

Note that $\lambda_0 s_{00}(\Lambda_{11}+\Lambda_{01})\Lambda_{10}\frac{\pi_0^*}{\pi_1^*}$

$$= \lambda_0 s_{00}\left(\frac{n_1\lambda_1 s_{11}}{m_1}+\frac{n_0\lambda_0 s_{01}}{m_1}\right)\frac{\lambda_1 n_1 s_{10} n_0}{m_0 n_1}$$
$$= \frac{\lambda_1 n_0 \lambda_0 s_{00}}{m_0}\left(\frac{n_1\lambda_1 s_{11}}{m_1}+\frac{n_1\lambda_1 s_{10}}{m_1}\right)s_{10}$$

as $n_0\lambda_0 s_{01} = n_1\lambda_1 s_{10}$

$$= \lambda_1\Lambda_{00}\frac{n_1\lambda_1 s_{10}}{m_1}$$

as $s_{11}+s_{10}=1$

$$= \lambda_1\Lambda_{00}\frac{n_0\lambda_0 s_{01}}{m_1}$$

as $n_0\lambda_0 s_{01} = n_1\lambda_1 s_{10}$ again

$$= \lambda_1\Lambda_{00}\Lambda_{01}.$$

Also

$$\lambda_0 s_{01}(\Lambda_{11}+\Lambda_{01})\frac{\pi_0^*}{\pi_1^*} = \frac{\lambda_0 s_{01} n_0}{n_1}\left(\frac{n_1\lambda_1 s_{11}}{m_1}+\frac{n_0\lambda_0 s_{01}}{m_1}\right)$$
$$= \frac{\lambda_0 s_{01} n_0}{n_1}\left(\frac{n_1\lambda_1 s_{11}}{m_1}+\frac{n_1\lambda_1 s_{10}}{m_1}\right)$$

as $n_0\lambda_0 s_{01} = n_1\lambda_1 s_{10}$ again

$$= \frac{\lambda_0 s_{01} n_0 \lambda_1}{m_1}$$
$$= \lambda_1\Lambda_{01}.$$

So

$$B\alpha_h = \frac{\lambda_1\alpha_h(1-\phi)^2\Lambda_{00}\Lambda_{01}+\lambda_1\alpha_h(\phi\Lambda_{00}+\Lambda_{10}+\tau)\Lambda_{01}(1-\phi)}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)-\Lambda_{01}\Lambda_{10}(1-\phi)^2}$$
$$= \frac{\lambda_1\alpha_h(1-\phi)\Lambda_{01}(\Lambda_{00}+\Lambda_{10}+\tau)}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)-\Lambda_{01}\Lambda_{10}(1-\phi)^2}$$
$$= \lambda_1 x^1.$$

Hence from (4.4.67) and (4.3.51) we deduce that $\boldsymbol{M}_{00}(\boldsymbol{0}) = k_{00}$. The results that the other entries of $\boldsymbol{M}(\boldsymbol{0})$ are the other entries of the transpose of the next generation

matrix follow similarly. All of the above work is completely different than that of Corson (2011) and Corson et al. (2013).

We need to show what happens when $0 \leq R_0 \leq 1$. In this part we will see that when R_0 takes these values then HCV will be eliminated in all PWIDs. This part of the proof follows the lines of the corresponding proof in Corson et al. (2013).

Lemma 4.4.1. *Suppose that $R_0 \leq 1$. The only non-negative solution $\boldsymbol{K}$ to $\boldsymbol{K=M(K)K}$ is $\boldsymbol{K=0}$.*

Proof. Using the method of Lemma 6.1 of Corson (2011) and Lemma 1 of Corson et al. (2013). □

We are now going to see what happens when $R_0 > 1$. We will now see that when $R_0 > 1$ there is a positive equilibrium which corresponds to a feasible equilibrium value for the model.

Theorem 4.4.2. *Assume that $R_0 > 1$ then the system given by (4.4.61) has one or more positive non-zero solution corresponding to a feasible equilibrium.*

If we let C denote the cone of positive vectors:

$$C = \big\{(K_0, K_1) : K_0 \geq 0, K_1 \geq 0\big\}.$$

This is obviously a cone since multiplying $\boldsymbol{K} = (K_0, K_1)$ by a scalar $\xi > 0$ results in a vector belonging to C. We use Theorem 1.6 of Gatica and Smith (1977) which is given in chapter 1 (Theorem 1.9.2) applied to the operator $T : C \to C$ given by $T(\boldsymbol{K}) = \boldsymbol{M}(\boldsymbol{K})\boldsymbol{K}$.

In order to apply this theorem exactly as in Corson (2011), 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 4.4.3. *$T(\boldsymbol{K})$ is continuous in $\boldsymbol{K}$ for all $\boldsymbol{K} \geq \boldsymbol{0}$.*

Proof. Proved in Lemma 6.2 of Corson (2011) and Lemma 2 of Corson et al. (2013). □

Note that we can consider a function as bounded if its range is a bounded set (Kreyszig (1978)).

Lemma 4.4.4. *$T(\boldsymbol{K}) : C \longrightarrow C$ is bounded.*

Proof. This proof is significantly different than in Corson (2011) and Corson et al. (2013). Now we need to prove that each of $M_{00}K_0 + M_{01}K_1$ and $M_{10}K_0 + M_{11}K_1$ is bounded in C.

$$\begin{aligned} M_{00}K_0 + M_{01}K_1 &= K_0 \\ &= \pi^0\Bigg[\lambda_0 s_{00}(1-\phi)\left(\frac{(\alpha_h - \alpha_y)B^0}{A^0} + \frac{\alpha_y D^0}{C^0}\right) \\ &\quad +\lambda_0 s_{01}(1-\phi)\left(\frac{(\alpha_h - \alpha_y)B^1}{A^1} + \frac{\alpha_y D^1}{C^1}\right)\Bigg]. \end{aligned}$$

If we define

$$\overline{\alpha}_h(\pi_h^0, \pi_h^1) = \frac{\Lambda_{10}\Lambda_{01}\left(1 - \frac{\pi_h^0}{\pi^0}\right)\left(1 - \frac{\pi_h^1}{\pi^1}\right)(1-\phi)^2}{\left(\Lambda_{00}\frac{\pi_h^0}{\pi^0} + \phi\Lambda_{00}\left(1 - \frac{\pi_h^0}{\pi^0}\right) + \Lambda_{10} + \tau\right)\left(\Lambda_{11}\frac{\pi_h^1}{\pi^1} + \phi\Lambda_{11}\left(1 - \frac{\pi_h^1}{\pi^1}\right) + \Lambda_{01} + \tau\right)}.$$

Then it is straightforward to show that

$$\frac{B^0}{A^0} \leq \frac{1}{1 - \overline{\alpha}_h(\pi_h^0, \pi_h^1)} \leq \frac{1}{1 - \overline{\alpha}_h(0,0)} \quad \text{and} \quad \frac{B^1}{A^1} \leq \frac{1}{1 - \overline{\alpha}_h(\pi_h^0, \pi_h^1)} \leq \frac{1}{1 - \overline{\alpha}_h(0,0)}.$$

Similarly defining

$$\overline{\alpha}_{hy}(\pi_{hy}^0, \pi_{hy}^1) = \frac{\Lambda_{10}\Lambda_{01}\left(1 - \frac{\pi_{hy}^0}{\pi^0}\right)\left(1 - \frac{\pi_{hy}^1}{\pi^1}\right)(1-\phi)^2}{\left(\Lambda_{00}\frac{\pi_{hy}^0}{\pi^0} + \phi\Lambda_{00}\left(1 - \frac{\pi_{hy}^0}{\pi^0}\right) + \Lambda_{10} + \tau\right)} \times \frac{1}{\left(\Lambda_{11}\frac{\pi_{hy}^1}{\pi^1} + \phi\Lambda_{11}\left(1 - \frac{\pi_{hy}^1}{\pi^1}\right) + \Lambda_{01} + \tau\right)},$$

where $\pi_{hy}^0 = \pi_h^0 + \pi_y^0$, $\pi_{hy}^1 = \pi_h^1 + \pi_y^1$, then

$$\frac{D^0}{C^0} \leq \frac{1}{1 - \overline{\alpha}_{hy}(\pi_{hy}^0, \pi_{hy}^1)} \leq \frac{1}{1 - \overline{\alpha}_{hy}(0,0)} \quad \text{and} \quad \frac{D^1}{C^1} \leq \frac{1}{1 - \overline{\alpha}_{hy}(\pi_{hy}^0, \pi_{hy}^1)} \leq \frac{1}{1 - \overline{\alpha}_{hy}(0,0)}.$$

Hence

$$M_{00}K_0 + M_{01}K_1 \leq \frac{A_1}{1-\overline{\alpha}_h(0,0)} + \frac{A_2}{1-\overline{\alpha}_{hy}(0,0)}$$

where $A_1 = \pi^0\lambda_0(1-\phi)(\alpha_h - \alpha_y)(s_{00}+s_{01})$ and $A_2 = \pi^0\lambda_0(1-\phi)\alpha_y(s_{00}+s_{01})$. In a similar way we have

$$\begin{aligned} M_{10}K_0 + M_{11}K_1 &= K_1 \\ &< \pi^1\Bigg[\lambda_1 s_{10}(1-\phi)\left(\frac{\alpha_h-\alpha_y}{1-\overline{\alpha}_h(0,0)} + \frac{\alpha_y}{1-\overline{\alpha}_{hy}(0,0)}\right) \\ &\quad +\lambda_1 s_{11}(1-\phi)\left(\frac{\alpha_h-\alpha_y}{1-\overline{\alpha}_h(0,0)} + \frac{\alpha_y}{1-\overline{\alpha}_{hy}(0,0)}\right)\Bigg] \\ &= \frac{B_1}{1-\overline{\alpha}_h(0,0)} + \frac{B_2}{1-\overline{\alpha}_{hy}(0,0)}, \end{aligned}$$

where $B_1 = \pi^1\lambda_1(1-\phi)(\alpha_h-\alpha_y)(s_{10}+s_{11})$ and $B_2 = \pi^1\lambda_1(1-\phi)\alpha_y(s_{10}+s_{11})$. Hence $T(\boldsymbol{K}) : C \longrightarrow C$ given by $T(\boldsymbol{K}) = \boldsymbol{M}(\boldsymbol{K})\boldsymbol{K}$ 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 (2017)). Hence $T(\boldsymbol{K})$ is a continuous compact operator. □

We are now going to prove that the operator $T(\boldsymbol{K})$ is Fréchet differentiable at $\boldsymbol{K} = \boldsymbol{0}$ in the direction of the cone C.

Lemma 4.4.5. *$T(\boldsymbol{K})$ 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. Proved in Lemma 6.4 of Corson (2011) and Lemma 4 of Corson et al. (2013). □

To apply Theorem 1.9.2 we need to prove that $T'(\boldsymbol{0})$ has an eigenvector corresponding to an eigenvalue $\omega_0 > 0$ and 1 is not an eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C. It is a straightforward conclusion to show the Fréchet derivative of T at $\boldsymbol{K} = \boldsymbol{0}$ is given by the transpose of the next generation matrix (4.3.52).

Since $T'(\boldsymbol{0})$ is a matrix with positive entries the modified model uses the Perron-Frobenius theory of positive matrices (Meyer (2000)). This theory shows us that there is a positive real numerical value 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 that corresponds 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 (c.f. Lemma 6.6 of Corson (2011) and Lemma 6 of Corson et al. (2013)).

Lemma 4.4.6. *If $R_0 > 1, T'(\boldsymbol{0})$ has an eigenvector $\boldsymbol{v} \in C$ and 1 is not eigenvalue of $T'(\boldsymbol{0})$ with corresponding eigenvector in C.*

We now prove condition (c) of the conditions immediately following Theorem 4.4.2.

Lemma 4.4.7. *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. Again using a similar proof as Lemma 6.6 of Corson (2011) and Lemma 6 of Corson et al. (2013).

This lemma completes the proof of the three conditions that are needed to apply Theorem 4.4.2 and we can conclude that when $R_0 > 1$ there exists a non-zero equilibrium $\boldsymbol{x}_0 \in C$. □

Now we need to prove that such an equilibrium value corresponds to a feasible endemic equilibrium for the full model. If each of the equilibrium values $\pi_x^{0*}, \pi_{x_1}^{0*}, \pi_{h_1}^{0*}$ $\ldots \pi_{h_2}^{1*}, \pi_y^{1*}$ and π_z^{1*} are positive then the endemic equilibrium value is feasible.

Setting $d/dt = 0$ in equation (4.2.29) we get

$$0 = \mu - (\mu + \eta)\pi_x^{0*} - \tilde{f}_0 \pi_x^{0*} + \psi \pi_y^{0*}.$$

Previously we know that $K_0^* = \pi_0^* \tilde{f}_0^*$, this leads to $\tilde{f}_0^* = K_0^*/\pi_0^*$. Therefore,

$$\pi_x^{0*} = \frac{\mu + \psi \pi_y^{0*}}{\mu + \eta + \frac{K_0^*}{\pi_0^*}}. \tag{4.4.68}$$

If we use a similar method as above with equations (4.2.30), (4.2.33) and (4.2.34) and using the relationships $\pi_{h_1}^{0*} = (1-\delta)\pi_h^{0*}$ and $\pi_{h_2}^{0*} = \delta \pi_h^{0*}$ we get

$$\pi_{x_1}^{0*} = \frac{\sigma(1-\alpha)\delta \pi_h^{0*}}{\mu + \eta + \frac{K_0^*}{\pi_0^*}}, \tag{4.4.69}$$

$$\pi_y^{0*} = \frac{\sigma(1-\delta)\pi_h^{0*}}{\mu + \eta + \psi}, \tag{4.4.70}$$

$$\pi_z^{0*} = \frac{\sigma\alpha\delta\pi_h^{0*}}{\mu + \eta}. \tag{4.4.71}$$

If $\boldsymbol{K}^* = \boldsymbol{M}(\boldsymbol{K}^*)\boldsymbol{K}^*$ corresponds to a non-zero equilibrium then it is obvious that both K_0^* and K_1^* must be strictly positive. From equation (4.4.58) we conclude that π_h^{0*} is strictly positive. Hence $\pi_x^{0*}, \pi_{x_1}^{0*}, \pi_y^{0*}$ and π_z^{0*} given by equations (4.4.68)-(4.4.71) are all strictly positive. Performing similar calculations with equations (4.2.35), (4.2.36), (4.2.39) and (4.2.40) and using the relationships $\pi_{h_1}^{1*} = (1-\delta)\pi_h^{1*}$ and $\pi_{h_2}^{1*} = \delta \pi_h^{1*}$ we get the following results:

$$\pi_x^{1*} = \frac{\eta \pi_x^{0*} + \psi \pi_y^{1*}}{\mu + \frac{K_1^*}{\pi_1^*}} \tag{4.4.72}$$

$$\pi_{x_1}^{1*} = \frac{\eta \pi_{x_1}^{0*} + \sigma(1-\alpha)\delta\pi_h^{1*}}{\mu + \frac{K_1^*}{\pi_1^*}}, \tag{4.4.73}$$

$$\pi_y^{1*} = \frac{\eta \pi_y^{0*} + \sigma(1-\delta)\pi_h^{1*}}{\mu + \psi}, \tag{4.4.74}$$

$$\pi_z^{1*} = \frac{\eta \pi_z^{0*} + \sigma\alpha\delta\pi_h^{1*}}{\mu}. \tag{4.4.75}$$

We know that $K_1^* > 0$ and from equation (4.4.60) $\pi_h^{1*} > 0$. This leads to $\pi_x^{1*}, \pi_{x_1}^{1*}, \pi_y^{1*}$ and π_z^{1*} given by equations (4.4.72)-(4.4.75) are all strictly positive. Also, if we are adding the equilibrium versions of equations (4.2.29)-(4.2.40) we conclude 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 endemic equilibrium value.

4.5 Global stability

We are now going to show the stability of the DFE when R_0 takes values between 0 and 1 inclusive.

Theorem 4.5.1. *When $R_0 \leq 1$ the DFE is globally asymptotically stable.*

Proof. This result will be shown in several stages using a method similar to that used in the proof of Theorem 2.4.2. We write $\pi_h^{0,\infty}$ for $\lim_{t\to\infty} \sup \pi_h^0(t)$, where $\pi_h^0(t) = \pi_{h_1}^0(t) + \pi_{h_2}^0(t)$, with similar definitions for the other $\pi_y^{0,\infty}, \pi_y^{1,\infty}$ and $\pi_h^{1,\infty}$, where $\pi_h^1(t) = \pi_{h_1}^1(t) + \pi_{h_2}^1(t)$. We will start the proof by giving several results that give upper bounds on the limit suprema $\pi_y^{0,\infty}, \pi_y^{1,\infty}, \pi_h^{0,\infty}$ and $\pi_h^{1,\infty}$. If we use equations (4.2.31), (4.2.32), (4.2.37) and (4.2.38) and derived relationships expressing $\pi_{h_1}^{0,\infty}, \pi_{h_2}^{0,\infty}, \pi_{h_1}^{1,\infty}$ and $\pi_{h_2}^{1,\infty}$ in terms of $\pi_h^{0,\infty}$ and $\pi_h^{1,\infty}$ this allows us to express our earlier results in terms of the two limit suprema $\pi_h^{0,\infty}$ and $\pi_h^{1,\infty}$. 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 4.5.2. $\left(\dfrac{\pi_h^0}{\pi^0}\right)^\infty \leq \dfrac{\pi_h^{0,\infty}}{\pi_0^*}$.

Proof. Recall that as pointed out earlier (4.2.3) $\pi^0 \to \pi_0^*$ as $t \to \infty$. Given $\epsilon > 0$ with $\frac{1}{2}\pi_0^* > \epsilon > 0$ there exists t_0 such that for all $t \geq t_0$ and $|\pi^0 - \pi_0^*| \leq \epsilon/2$, we have

$$\pi_h^0 \leq \pi_h^{0,\infty} + \frac{\epsilon}{2}\pi_0^*.$$

Therefore, for all $t \geq t_0$, $\pi^0 \geq \pi_0^* - \epsilon/2 \geq \frac{3}{4}\pi_0^*$,

$$\begin{aligned}
\frac{\pi_h^0}{\pi^0} - \frac{\pi_h^{0,\infty}}{\pi_0^*} &= \frac{\pi_h^0\pi_0^* - \pi_h^{0,\infty}\pi^0}{\pi^0\pi_0^*}, \\
&\leq \frac{\pi_h^0(\pi_0^* - \pi^0) + \pi^0(\pi_h^0 - \pi_h^{0,\infty})}{\pi^0\pi_0^*} \\
&\leq \frac{\epsilon/2}{\pi^0\pi_0^*} + \epsilon/2 \\
&\leq \frac{4}{3\pi_0^{*2}}\epsilon/2 + \epsilon/2 \\
&= \frac{\epsilon}{2}\left(\frac{4}{3\pi_0^{*2}} + 1\right).
\end{aligned}$$

So given $\epsilon_1 > 0$ choose $\epsilon = \frac{\epsilon_1}{\frac{1}{2}\left(\frac{4}{3\pi_0^{*2}}+1\right)}$, then with this value of ϵ for $t \geq t_0$ we have that

$$\frac{\pi_h^0}{\pi^0} \leq \frac{\pi_h^{0,\infty}}{\pi_0^*} + \epsilon_1.$$

Hence

$$\left(\frac{\pi_h^0}{\pi^0}\right)^\infty \leq \frac{\pi_h^{0,\infty}}{\pi_0^*} + \epsilon_1.$$

But as ϵ_1 is arbitrary then

$$\left(\frac{\pi_h^0}{\pi^0}\right)^\infty \leq \frac{\pi_h^{0,\infty}}{\pi_0^*}.$$

Similarly we conclude that

$$\left(\frac{\pi_h^1}{\pi^1}\right)^\infty \leq \frac{\pi_h^{1,\infty}}{\pi_1^*}.$$

□

Lemma 4.5.3.

$$\pi_h^{0,\infty} \leq \frac{\overline{K}_0}{\mu+\sigma+\eta+\frac{\overline{K}_0}{\pi_0^*}},$$

where $\overline{K}_0 = \alpha_h A\pi_h^{0,\infty} + \alpha_y A\pi_y^{0,\infty} + \alpha_h B\pi_h^{1,\infty} + \alpha_y B\pi_y^{1,\infty}$,

$$A = \frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{00}+\Lambda_{10})}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)} + \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{00}+\Lambda_{10})\Lambda_{01}(1-\phi)}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)}$$

$$B = \frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{11}+\Lambda_{01})\Lambda_{10}(1-\phi)\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)} + \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{11}+\Lambda_{01})\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{11}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)} \tag{4.5.76}$$

and $\overline{\alpha}_h^* = \dfrac{\Lambda_{01}\Lambda_{10}(1-\phi)^2}{(\phi\Lambda_{00}+\Lambda_{01}+\tau)(\phi\Lambda_{11}+\Lambda_{10}+\tau)}$.

Proof. Write $\beta_{hy}^0 = \beta_h^0 + \beta_y^0$ and $\beta_{hy}^1 = \beta_h^1 + \beta_y^1$, similarly for π_{hy}^0 and π_{hy}^1. Using equations (4.2.31) and (4.2.32) together we have

$$\begin{aligned}
\frac{d\pi_h^0}{dt} &= \Big[\lambda_0 s_{00}(1-\phi)\big((\alpha_h-\alpha_y)\beta_h^0 + \alpha_y\beta_{hy}^0\big) + \lambda_0 s_{01}(1-\phi)\big((\alpha_h-\alpha_y)\beta_h^1 + \alpha_y\beta_{hy}^1\big)\Big] \\
&\quad \times(\pi^0 - \pi_h^0 - \pi_y^0 - \pi_z^0) - (\mu+\sigma+\eta)\pi_h^0, \\
&= \pi^0\Big[\lambda_0 s_{00}(1-\phi)\big((\alpha_h-\alpha_y)\beta_h^0 + \alpha_y\beta_{hy}^0\big) + \lambda_0 s_{01}(1-\phi)\big((\alpha_h-\alpha_y)\beta_h^1 + \\
&\quad \alpha_y\beta_{hy}^1\big)\Big]\left(1 - \frac{1}{\pi^0}(\pi_h^0 + \pi_y^0 + \pi_z^0)\right) - (\mu+\sigma+\eta)\pi_h^0,
\end{aligned}$$

$$\leq \pi^0\Big[\lambda_0 s_{00}(1-\phi)\big((\alpha_h-\alpha_y)\beta_h^0+\alpha_y\beta_{hy}^0\big)+\lambda_0 s_{01}(1-\phi)\big((\alpha_h-\alpha_y)\beta_h^1+\alpha_y\beta_{hy}^1\big)\Big]$$
$$\times\left(1-\frac{\pi_h^0}{\pi^0}\right)-(\mu+\sigma+\eta)\pi_h^0. \tag{4.5.77}$$

Note that by adding (4.2.17) to (4.2.18) for Assumption 1 or (4.2.19) to (4.2.20) for Assumption 2 and using the relationship $\Lambda_{01}\frac{m_1}{m_0}=\Lambda_{10}$

$$\frac{d\beta_h^0}{dt}=\Lambda_{00}\frac{\pi_h^0}{\pi^0}(1-\beta_h^0)+\Lambda_{10}\frac{\pi_h^0}{\pi^0}-\phi\Lambda_{00}\left(1-\frac{\pi_h^0}{\pi^0}\right)\beta_h^0-\Lambda_{10}\beta_h^0+\Lambda_{10}\left(1-\frac{\pi_h^0}{\pi^0}\right)\beta_h^1(1-\phi)$$
$$-\tau\beta_h^0.$$

Hence $\exists\ t_0$ so that for $t\geq t_0$

$$\frac{d\beta_h^0}{dt}\leq(\Lambda_{00}+\Lambda_{10})\frac{\pi_h^0}{\pi^0}+\Lambda_{10}\beta_h^{1,\infty}(1-\phi)+\epsilon-(\phi\Lambda_{00}+\Lambda_{10}+\tau)\beta_h^0.$$

Hence using Lemma 4.5.2 and a similar argument as in the proof of Lemma 2.3.3

$$\beta_h^{0,\infty}\leq\frac{(\Lambda_{00}+\Lambda_{10})\frac{\pi_h^{0,\infty}}{\pi_0^*}+\Lambda_{10}\beta_h^{1,\infty}(1-\phi)}{\phi\Lambda_{00}+\Lambda_{10}+\tau},$$

similarly

$$\beta_h^{1,\infty}\leq\frac{(\Lambda_{11}+\Lambda_{01})\frac{\pi_h^{1,\infty}}{\pi_1^*}+\Lambda_{01}\beta_h^{0,\infty}(1-\phi)}{\phi\Lambda_{11}+\Lambda_{01}+\tau}.$$

Putting these results together

$$\beta_h^{0,\infty}\leq\frac{(\Lambda_{00}+\Lambda_{10})\frac{\pi_h^{0,\infty}}{\pi_0^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)}+\frac{\Lambda_{10}(1-\phi)(\Lambda_{11}+\Lambda_{01})\frac{\pi_h^{1,\infty}}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)},$$

$$\beta_h^{1,\infty}\leq\frac{(\Lambda_{11}+\Lambda_{01})\frac{\pi_h^{1,\infty}}{\pi_1^*}}{(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)}+\frac{\Lambda_{01}(1-\phi)(\Lambda_{00}+\Lambda_{10})\frac{\pi_h^{0,\infty}}{\pi_0^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)}.$$

Similarly, we have that

$$\beta_{hy}^{0,\infty}\leq\frac{(\Lambda_{00}+\Lambda_{10})\frac{\pi_{hy}^{0,\infty}}{\pi_0^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)}+\frac{\Lambda_{10}(1-\phi)(\Lambda_{11}+\Lambda_{01})\frac{\pi_{hy}^{1,\infty}}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)}.$$

$$\beta_{hy}^{1,\infty}\leq\frac{(\Lambda_{11}+\Lambda_{01})\frac{\pi_{hy}^{1,\infty}}{\pi_1^*}}{(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)}+\frac{\Lambda_{01}(1-\phi)(\Lambda_{00}+\Lambda_{11})\frac{\pi_{hy}^{0,\infty}}{\pi_0^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)}.$$

These last two results are true because Lemma 4.5.2 works equally for π^0_{hy} and π^1_{hy} as π^0_h and π^1_h. Recall that $\pi_0 \to \pi^*_0$ as $t \to \infty$. Hence from (4.5.76) and (4.5.77) given $\epsilon > 0$ $\exists$ t_1 such that for $t \geq t_1$

$$\frac{d\pi^0_h}{dt} \leq \pi^*_0\left(1 - \frac{\pi^0_h}{\pi^*_0}\right)\left(\frac{\overline{K}_0}{\pi^*_0} + \epsilon\right) - (\mu + \sigma + \eta)\pi^0_h.$$

Hence using a similar argument to the proof of Lemma 2.3.3

$$\pi^{0,\infty}_h \leq \frac{\overline{K}_0 + \epsilon\pi^*_0}{\mu + \sigma + \eta + \frac{\overline{K}_0}{\pi^*_0} + \epsilon}.$$

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

$$\pi^{0,\infty}_h \leq \frac{\overline{K}_0}{\mu + \sigma + \eta + \frac{\overline{K}_0}{\pi^*_0}}.$$

□

Similarly, we have the following result:

Lemma 4.5.4.

$$\pi^{1,\infty}_h \leq \frac{\overline{K}_1 + \eta\pi^{0,\infty}_h}{\mu + \sigma + \frac{\overline{K}_1}{\pi^*_1}},$$

where

$$\overline{K}_1 = A_1(\alpha_h\pi^{0,\infty}_h + \alpha_y\pi^{0,\infty}_y) + B_1(\alpha_h\pi^{1,\infty}_h + \alpha_y\pi^{1,\infty}_y),$$
$$A_1 = \frac{\lambda_1 s_{10}(1-\phi)(\Lambda_{00} + \Lambda_{10})\frac{\pi^*_1}{\pi^*_0}}{(\phi\Lambda_{00} + \Lambda_{10} + \tau)(1 - \overline{\alpha}^*_h)} + \frac{\lambda_1 s_{11}(1-\phi)\Lambda_{01}(\Lambda_{00} + \Lambda_{10})(1-\phi)\frac{\pi^*_1}{\pi^*_0}}{(\phi\Lambda_{00} + \Lambda_{10} + \tau)(\phi\Lambda_{11} + \Lambda_{01} + \tau)(1 - \overline{\alpha}^*_h)}$$

and

$$B_1 = \frac{\lambda_1 s_{10}(1-\phi)\Lambda_{10}(\Lambda_{11} + \Lambda_{10})(1-\phi)}{(\phi\Lambda_{00} + \Lambda_{10} + \tau)(\phi\Lambda_{11} + \Lambda_{01} + \tau)(1 - \overline{\alpha}^*_h)} + \frac{\lambda_1 s_{11}(1-\phi)(\Lambda_{11} + \Lambda_{01})}{(\phi\Lambda_{11} + \Lambda_{01} + \tau)(1 - \overline{\alpha}^*_h)}. \tag{4.5.78}$$

Proof. Taking equations (4.2.37) and (4.2.38) along with the method used in the proof of Lemma 4.5.3 the result follows. □

It is useful to use the same techniques used to prove Lemma 2.3.3 to prove results that give upper bounds on the limit suprema of π^0_y and π^1_y in terms of $\pi^{0,\infty}_{h_1}$ and $\pi^{1,\infty}_{h_1}$.

Lemma 4.5.5.

$$\pi_y^{0,\infty} \leq \frac{\sigma \pi_{h_1}^{0,\infty}}{\mu + \eta + \psi}.$$

Proof. Using equation (4.2.33) we have,

$$\frac{d\pi_y^0}{dt} = \sigma \pi_{h_1}^0 - (\mu + \eta + \psi)\pi_y^0.$$

Given $\epsilon > 0$, we have that

$$\pi_{h_1}^0 \leq \pi_{h_1}^{0,\infty} + \epsilon, \qquad \forall t \geq t_3(\epsilon).$$

$$\frac{d}{dt}[\pi_y^0 \exp((\mu + \eta + \psi)t)] \leq \sigma(\pi_{h_1}^{0,\infty} + \epsilon)\exp((\mu + \eta + \psi)t), \qquad \forall t \geq t_3(\epsilon).$$

Integrating over $[t_3(\epsilon), t]$ gives

$$\pi_y^0(t) \leq \epsilon + \frac{\sigma(\pi_{h_1}^{0,\infty} + \epsilon)}{\mu + \eta + \psi} \quad \forall t \geq t_4(\epsilon) \text{ for some } t_4(\epsilon) > t_3(\epsilon) \text{ sufficiently large.}$$

Using the lim sup and letting $t \to \infty$ we have

$$\pi_y^{0,\infty} \leq \frac{\sigma \pi_{h_1}^{0,\infty}}{\mu + \eta + \psi} + \epsilon_1, \qquad \text{where } \epsilon_1 = \epsilon\left(\frac{\mu + \eta + \psi + \sigma}{\mu + \eta + \psi}\right).$$

Since $\epsilon_1 > 0$ is arbitrary, the result follows. □

Lemma 4.5.6.

$$\pi_y^{1,\infty} \leq \frac{\sigma \pi_{h_1}^{1,\infty}}{\mu + \psi} + \frac{\sigma \eta \pi_{h_1}^{0,\infty}}{(\mu + \psi)(\mu + \psi + \eta)}.$$

Proof. Taking equation (4.2.39) along with the method used in the proof of Lemma 4.5.5 the result follows. □

We now going to use equations (4.2.31) and (4.2.32) to find a relationship between $\pi_{h_1}^{0,\infty}$ and $\pi_{h_2}^{0,\infty}$.

Lemma 4.5.7. $(1 - \delta)\pi_{h_2}^{0,\infty} = \delta \pi_{h_1}^{0,\infty}$.

Proof. As proved in Lemma 6.13 of Corson (2011) and Lemma 13 in Corson (2013).

□

Lemma 4.5.8. $(1 - \delta)\pi_{h_2}^{1,\infty} = \delta \pi_{h_1}^{1,\infty}$.

Proof. From equations (4.2.37) and (4.2.38)

$$\begin{aligned}\frac{d}{dt}\left(\frac{\pi^1_{h_1}}{1-\delta}-\frac{\pi^1_{h_2}}{\delta}\right) &= \eta\left(\frac{\pi^0_{h_1}}{1-\delta}-\frac{\pi^0_{h_2}}{\delta}\right)-(\mu+\sigma)\left(\frac{\pi^1_{h_1}}{1-\delta}-\frac{\pi^1_{h_2}}{\delta}\right),\\ &= \eta\left(\frac{\pi^0_{h_1}(0)}{1-\delta}-\frac{\pi^0_{h_2}(0)}{\delta}\right)\exp[-(\mu+\sigma+\eta)t]\\ &\quad -(\mu+\sigma)\left(\frac{\pi^1_{h_1}}{1-\delta}-\frac{\pi^1_{h_2}}{\delta}\right).\end{aligned}$$

Hence

$$\frac{d}{dt}\left[\left(\frac{\pi^1_{h_1}}{1-\delta}-\frac{\pi^1_{h_2}}{\delta}\right)\exp[(\mu+\sigma)t\right]=\eta\left(\frac{\pi^0_{h_1}(0)}{1-\delta}-\frac{\pi^0_{h_2}(0)}{\delta}\right)\exp[-\eta t].$$

Solving

$$\begin{aligned}\frac{\pi^1_{h_1}}{1-\delta}-\frac{\pi^1_{h_2}}{\delta} &= \left(\frac{\pi^0_{h_1}(0)}{1-\delta}-\frac{\pi^0_{h_2}(0)}{\delta}\right)(1-\exp[-\eta t])\exp[-(\mu+\sigma)t]\\ &\quad +\left(\frac{\pi^1_{h_1}(0)}{1-\delta}-\frac{\pi^1_{h_1}(0)}{\delta}\right)\exp[-(\mu+\sigma)t].\end{aligned}$$

Hence $\dfrac{\pi^1_{h_1}}{1-\delta}-\dfrac{\pi^1_{h_2}}{\delta}\to 0$ as $t\to\infty$. So we deduce that $\delta\pi^{1,\infty}_{h_1}=(1-\delta)\pi^{1,\infty}_{h_2}$ similarly to Lemma 4.5.7. □

Write $\pi^0_h=\pi^0_{h_1}+\pi^0_{h_2}$. As we have $\delta\pi^0_{h_1}-(1-\delta)\pi^0_{h_2}\to 0$ as $t\to\infty$ it is straightforward to show that $\pi^{0,\infty}_h=\pi^{0,\infty}_{h_1}/(1-\delta)=\pi^{0,\infty}_{h_2}/\delta$. It is similarly straightforward to show that $\pi^{1,\infty}_h=\pi^{1,\infty}_{h_1}/(1-\delta)=\pi^{1,\infty}_{h_2}/\delta$. We can use these results to define the inequalities in Lemmas 4.5.5 and 4.5.6 in terms of $\pi^{0,\infty}_h$ and $\pi^{1,\infty}_h$ to get:

$$\pi^{0,\infty}_y \leq \frac{\sigma(1-\delta)\pi^{0,\infty}_h}{\mu+\eta+\psi}. \tag{4.5.79}$$

$$\pi^{1,\infty}_y \leq \frac{\sigma(1-\delta)\pi^{1,\infty}_h}{\mu+\psi}+\frac{\sigma\eta(1-\delta)\pi^{0,\infty}_h}{(\mu+\psi)(\mu+\psi+\eta)}. \tag{4.5.80}$$

Substituting into equations (4.5.76) and (4.5.78)

$$\begin{aligned}\overline{K}_0 &\leq A\pi^{0,\infty}_h\left(\alpha_h+\frac{\alpha_y\sigma(1-\delta)}{\mu+\eta+\psi}\right)\\ &\quad + B\left(\pi^{1,\infty}_h\left(\alpha_h+\frac{\alpha_y\sigma(1-\delta)}{\mu+\psi}\right)+\pi^{0,\infty}_h\frac{\eta\sigma(1-\delta)\alpha_y}{(\mu+\psi)(\mu+\eta+\psi)}\right).\end{aligned} \tag{4.5.81}$$

$$\begin{aligned}\overline{K}_1 &\leq A_1\pi^{0,\infty}_h\left(\alpha_h+\frac{\alpha_y\sigma(1-\delta)}{\mu+\eta+\psi}\right)\\ &\quad + B_1\left(\pi^{1,\infty}_h\left(\alpha_h+\frac{\alpha_y\sigma(1-\delta)}{\mu+\psi}\right)+\pi^{0,\infty}_h\frac{\eta\sigma(1-\delta)\alpha_y}{(\mu+\psi)(\mu+\eta+\psi)}\right).\end{aligned}$$

Recall that

$$\begin{aligned}
A &= \frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{00}+\Lambda_{10})}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)} + \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{00}+\Lambda_{10})\Lambda_{01}(1-\phi)}{(\phi\Lambda_{11}+\Lambda_{01}+\tau)(\phi\Lambda_{00}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)},\\
B &= \frac{\lambda_0 s_{00}(1-\phi)(\Lambda_{11}+\Lambda_{01})\Lambda_{10}\frac{\pi_0^*}{\pi_1^*}(1-\phi)}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)} + \frac{\lambda_0 s_{01}(1-\phi)(\Lambda_{11}+\Lambda_{01})\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)},
\end{aligned}$$

$$\begin{aligned}
A_1 &= \frac{\lambda_1 s_{10}(1-\phi)(\Lambda_{00}+\Lambda_{10})\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(1-\overline{\alpha}_h^*)} + \frac{\lambda_1 s_{11}(1-\phi)\Lambda_{01}(\Lambda_{00}+\Lambda_{10})(1-\phi)\frac{\pi_0^*}{\pi_1^*}}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)},\\
B_1 &= \frac{\lambda_1 s_{10}(1-\phi)(\Lambda_{11}+\Lambda_{01})\Lambda_{10}(1-\phi)}{(\phi\Lambda_{00}+\Lambda_{10}+\tau)(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)} + \frac{\lambda_1 s_{11}(1-\phi)(\Lambda_{11}+\Lambda_{01})}{(\phi\Lambda_{11}+\Lambda_{01}+\tau)(1-\overline{\alpha}_h^*)}.
\end{aligned}$$

Substituting in the upper bounds for $\pi_h^{0,\infty}$ and $\pi_h^{1,\infty}$ given by Lemmas 4.5.3 and 4.5.4 respectively allows us to define this as a set of simultaneous inequalities satisfied by

$$\overline{\boldsymbol{K}} \leq \boldsymbol{M}^+(\overline{\boldsymbol{K}})\overline{\boldsymbol{K}},$$

where $\boldsymbol{M}^+(\overline{\boldsymbol{K}})$ is a strictly positive function of $\overline{\boldsymbol{K}}$ for $\overline{\boldsymbol{K}} \geq \boldsymbol{0}$ with $M_{ij}^+(\overline{\boldsymbol{K}}) = M_{ij}^+(\overline{K}_0, \overline{K}_1) \geq 0$. If $\overline{\boldsymbol{K}} > 0$ but either $\overline{K}_0 > 0$ or $\overline{K}_1 > 0$ then $M_{ij}^+(\overline{\boldsymbol{K}}) < M_{ij}^+(\boldsymbol{0})$. Moreover $\boldsymbol{M}^+(\boldsymbol{0}) = \boldsymbol{M}(\boldsymbol{0})$, the transpose of the next generation matrix (4.3.52). Hence, assuming that either $\overline{K}_0 > 0$ or $\overline{K}_1 > 0$ we have

$$\overline{\boldsymbol{K}} < \boldsymbol{M}(\boldsymbol{0})\overline{\boldsymbol{K}}, \tag{4.5.82}$$

with strict inequality in both components. Since $\overline{\boldsymbol{K}}$ is a positive vector in (4.5.82) there exists an $\epsilon > 0$ with

$$\overline{\boldsymbol{K}}(1+\epsilon) < \boldsymbol{M}(\boldsymbol{0})\overline{\boldsymbol{K}}.$$

Hence arguing as in Corson et al. (2013) we deduce

$$(1+\epsilon) < ||\boldsymbol{M}^n(\boldsymbol{0})||^{\frac{1}{n}}. \tag{4.5.83}$$

Again as in Corson et al. (2013) we also use the fact that the spectral radius, ρ, of a matrix $\boldsymbol{M}$ is given by $\lim_{t\to\infty} ||\boldsymbol{M}^n||^{\frac{1}{n}}$ (Diekmann and Heesterbeek (2000)), we let $n \to \infty$ in (4.5.83) to get

$$\rho(\boldsymbol{M}(\boldsymbol{0})) \geq 1+\epsilon,$$

where $\rho(\boldsymbol{M}(\boldsymbol{0}))$ represents to the spectral radius of the matrix $\boldsymbol{M}(\boldsymbol{0})$. Thus, the spectral radius of $\boldsymbol{M}(\boldsymbol{0})$ is equal to the basic reproductive number R_0, this shows that $R_0 \geq 1 + \epsilon$. So this leads us to a contradiction and so $\overline{K}_0 = \overline{K}_1 = 0$ leads to $\pi_h^{0,\infty} = \pi_h^{1,\infty} = 0$ when $R_0 \leq 1$. $\pi_h^{0,\infty} = \pi_h^{1,\infty} = 0$ shows that $\pi_{h_1}^{0,\infty} = \pi_{h_2}^{0,\infty} = \pi_y^{0,\infty} = \pi_{h_1}^{1,\infty} = \pi_{h_2}^{1,\infty} = \pi_y^{1,\infty} = 0$. Also this result shows 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 is the completion of our proof for the global stability of the DFE when R_0 between 0 and 1.

Note that this proof worked for the original model (4.5)-(4.27) with separate equations for the PWIDs and the needles and syringes. However it is straightforward to adapt it to the approximate model (4.28) to (4.44) to give the same result.

4.6 Parameters and numerical simulations

The aim of this section is to use the simulation package Wolfram Mathematica version 11.1 to come up with hepatitis C virus (HCV) prevalence estimates. These estimates are meant to assess the Glasgow PWID population over time, according to the model equations in Chapter 3. We shall base our estimates on those of Corson et al. (2013) and here briefly summarise the values and to achieve this feat, we use the Glasgow PWID survey data collected between 1990-1993 and 2008-2009. From this data, through HPS, one is then able to find two sets of parameter approximations. Each of these approximated figures shows the PWID behaviour as it was between the years 1990-1993 and 2008-2009, respectively. In order to produce these HCV prevalence estimates, one selects each parameter set individually and relates it with the estimated hepatitis C prevalence of the selected people who inject drugs (PWIDs) surveyed in Glasgow within that particular time frame. This research aims to prove that although the model created produces positive results based on the earlier data; it fails miserably when the more recent survey data acquired is applied to find the similar parameter estimates. Additionally, as PWIDs tend to underrate their syringe and needle sharing habits (Greenfield et al. (1995)) further investigations are in order to determine to what extent this occurrence transpires among Glasgow PWIDs in

the period between 2008-2009.

4.6.1 Parameters

In Tables 4.1, 4.2 and 4.3 the data presented here illustrates the parameter estimates applied to the simulations in this research. The focus now lies on the estimates used in our test simulations, not taking into account the values of $\alpha, \delta, \sigma, \psi$ and ϕ. These values will remain constant all the way through our simulations. This is a quality they will possess beginning all the way from our simple model simulations (for further clarification on these estimates, see Chapter 2).

From surveillance carried out by a collaboration of HPS and colleagues (Rehm et al. (2010)), it was found that PWIDs fall into two experience groups. This separation is based on the difference witnessed from the period where they start injections (Corson (2011) and Corson et al. (2013)). The threshold dividing the two sets of people is 3 to 5 years of time difference. This difference in years helps researchers to have at least two different levels which are made up of beginners who have been injecting for five years or less and seasoned PWIDs who have injected for five years or more. Therefore as in Corson (2011) and Corson et al. (2013), this data set is represented as $1/\eta = 5$ years.

Corson (2011) and Corson et al. (2013) project that 33.33% of the entire Glasgow PWID population are relatively recently started and new injectors while at least 66.67% are much older seasoned injectors especially according to the information collected between the years 1990-1993 and 2008-2009. Moreover, the PWID population in Glasgow has remained relatively constant over the years. With this assumption in mind, one can, therefore, assume that the estimates for π^0 and π^1 can be applied as the equilibrium values for these parameters. That is, $\pi^0 = \pi_0^* = 0.3333$ and $\pi^1 = \pi_1^* = 0.6667$.

We follow Corson (2011) and Corson et al. (2013) to approximate that for the time between 1990-1993 $s_{00} = 0.6667,\ s_{01} = 0.3333,\ s_{10} = 0.2026$ and $s_{11} = 0.7974$ and for the time between 2008-2009 $s_{00} = 0.6667,\ s_{01} = 0.3333,\ s_{10} = 0.1276$ and $s_{11} = 0.8724$.

Again we follow Corson (2011) and Corson et al. (2013) to estimate the aver-

age working life of a needle is $(365.25/\tau)$ during two different periods of time. One period of time is from 1990 to 1993 and another period is from 2008 to 2009. Therefore $2,038$ Glasgow PWIDs were assessed between the period 1990-1993 and from this data Corson (2011) and Corson et al. (2013) estimate the working lifespan of a needle to be around 15.4 days. Another estimation was based on the 704 Glasgow PWIDs surveyed from June 2008 to June 2009 and from this data Corson (2011) and Corson et al. (2013) estimate the working lifespan of a needle to be 3.26 days.

According to Corson (2011) and Corson (2013) between the period 1990-1993 the average injection rate for newly started PWIDs (λ_0) is 45 shared injections for each PWID every year and for experienced PWIDs (λ_1) is 37 shared injections for each PWID. Moreover, between the period 2008-2009 the average injection rate of recently started PWIDs (λ_0) is 1.96 annually with shared injections for seasoned PWIDs (λ_1) at 2.56 annually.

Similar to Corson's research, we too increased our estimates for a chance for transmission of chronic infection from $\alpha_y = 0.016$ to $\alpha_y = 0.025$. This move aimed to match the change of estimates proposed by Crofts et al. (1999) (0.013-0.049), Hutchinson et al. (2006a), the Advisory Council on the Misuse of Drugs (2009) (0.015-0.05) and Bird et al. (2006) (0.02-0.03). As per the assumption, one applies the 2.7 times higher rate of acute HCV infection over chronic infection to determine later the value of $\alpha_y = 0.025$ which implies that, α_h, as per the injection transmission chance of acute HCV infection to be 0.0675.

4.6.2 Simulation results

We now use Wolfram Mathematica version 11.1 to produce HCV prevalence estimates for each period provided in the Tables 4.1, 4.2 and 4.3 together with the parameters within and bearing in mind the rate of treatment $\psi = 0.1$ per year, research simulates transmission of HCV to be over a 70 year period. Initially the assumption is that 50% of the PWID participants already have acute HCV (h_1) and no other PWIDs have the disease. To clarify further, $\pi_x^0(0) = 0.5/3, \pi_{x_1}^0(0) = 0, \pi_{h_1}^0(0) = 0.5/3, \pi_{h_2}^0(0) = 0, \pi_y^0(0) = 0, \pi_z^0(0) = 0, \pi_x^1(0) = 1/3, \pi_{x_1}^1(0) = 0, \pi_{h_1}(0) = 1/3, \pi_{h_2}^1(0) = 0, \pi_y^1(0) = 0$ and $\pi_z^1(0) = 0$ where $\pi_x^0(0) = 0$ represents the portion

of PWIDs that are young and inexperienced in the group and x-susceptible at time $t = 0$.

Parameter	Estimate	Source	Notes
ϕ	0.255	Unpublished data HPS (1990-1993)	Observed data on Glasgow PWIDs during 1990-1993
α_y	2.5%	Hutchinson et al. (2006a)	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 PWIDs
$1/\mu$	10.002 years	Calculated estimate	Based on assumed equilibrium proportion of naive PWIDs and time since onset of injection
π^0	0.3333	Unpublished data HPS (2008-2009)	Based on observed data of Glasgow PWIDs during 2008-2009
π^1	0.6667	Unpublished data HPS (2008-2009)	Based on observed data of Glasgow PWIDs during 2008-2009
ψ	0.1 per year	Conservative estimate	No data

Table 4.1: Table of baseline parameter estimates for use in the time since onset of injection model. (Adapted from Corson et al. (2013)).

Parameter	Estimate	Source	Notes
λ_0	45 per PWID per year	Unpublished data HPS (1990-1993)	Observed data on Glasgow PWIDs during 1990-1993
λ_1	37 per PWID per year	Unpublished data HPS (1990-1993)	Observed data on Glasgow PWIDs 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 PWIDs 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 4.2: Table of parameter estimates for the period 1990-1993. (Adapted from Corson et al. (2013)).

Parallel explanations are available for the other PWID classes. The assumption in play here is that the section of individuals in the recently started and seasoned groups begin at their balance values. This ensures that the conditions and values are satisfied. This value then suggests that the needles and syringes present in each group stays constant. The overall prevalence of HCV (given by $\pi^0_{x_1}+\pi^0_{h_1}+\pi^0_{h_2}+\pi^0_y+\pi^0_z+\pi^0_{x_1}+\pi^1_{h_1}+\pi^1_{h_2}+\pi^1_y+\pi^1_z$) is illustrated in Figures 4.1 and 4.2. These conditions were selected since they allow one to view the performance of the model under the sets of parameters present. In Figure 4.1 one can eventually arrive at a stable state resolution. When one applies the baseline parameter values used in the year 1990-1993 (Table 4.2), $R_0 = 6.177 > 1$ the occurrence of HCV among Glasgow PWIDs reaches an incidence of roughly 81%. Also, in Figure 4.2 it is clear that HCV occurrence reaches a stable state resolution. However, once the model is applied to the parameter estimates from the year 2008-2009 (Table 4.2),

$R_0 = 0.0275 < 1$ the results suggest a marked reduction in HCV frequency in Glasgow PWIDs. This phenomenon results in the elimination of HCV.

Parameter	Estimate	Source	Notes
λ_0	1.96 per PWID per year	Unpublished data HPS (2008-2009)	Observed data on Glasgow PWIDs during 2008-2009
λ_1	2.56 per PWID per year	Unpublished data HPS (2008-2009)	Observed data on Glasgow PWIDs during 2008-2009
$365.25/\tau$	3.26 days	Hay et al. (2009); ISD Scotland (2010)	Based on the estimated number of Glasgow PWIDs 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 4.3: Table of parameter estimates for the period 2008-2009. (Adapted from Corson et al. (2013)).

4.6.3 Parameter combinations resulting in $R_0 \leq 1$.

We have seen that the health organisations would need to distribute approximately 3.2 times more needles to PWIDs to get the $R_0 = 1$ target, it is also very important to achieve $R_0 < 1$. It is possible that a smaller increase in needle turnover combined with another parameter will result in PWIDs and needles arriving to a disease free state in a shorter time frame. In this subsection we will focus on combining parameters and finding the range of values that allow for $R_0 < 1$.

Figures 4.3, 4.4 and 4.5 clearly show the combinations that will result in $R_0 \leq 1$

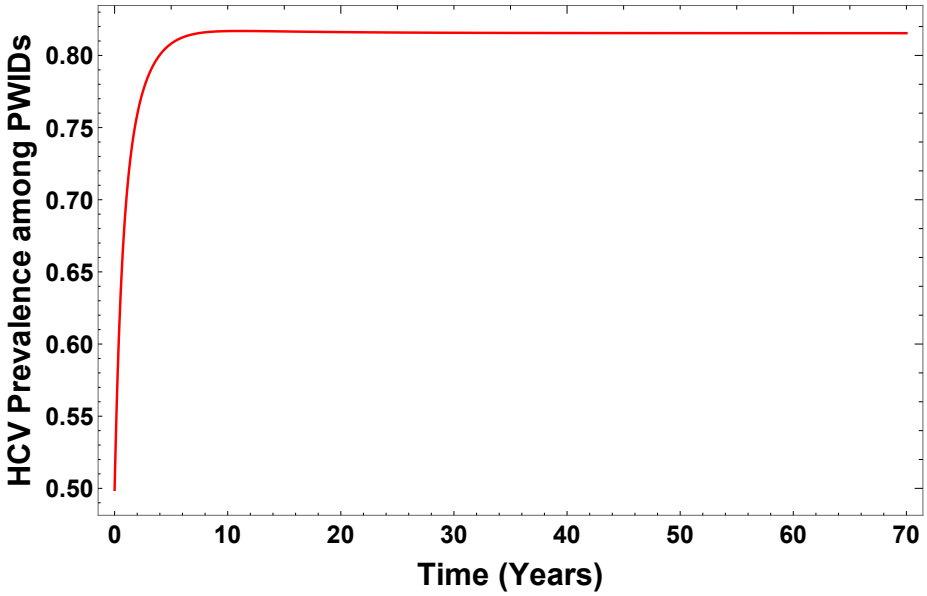

Figure 4.1: HCV prevalence using baseline parameter estimates for 1990-1993.

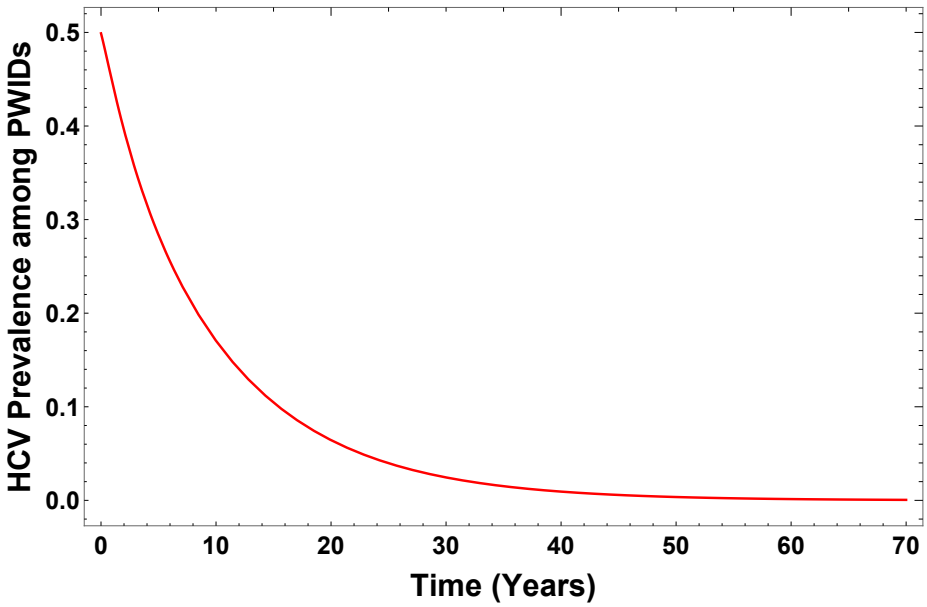

Figure 4.2: HCV prevalence using baseline parameter estimates for 2008-2009.

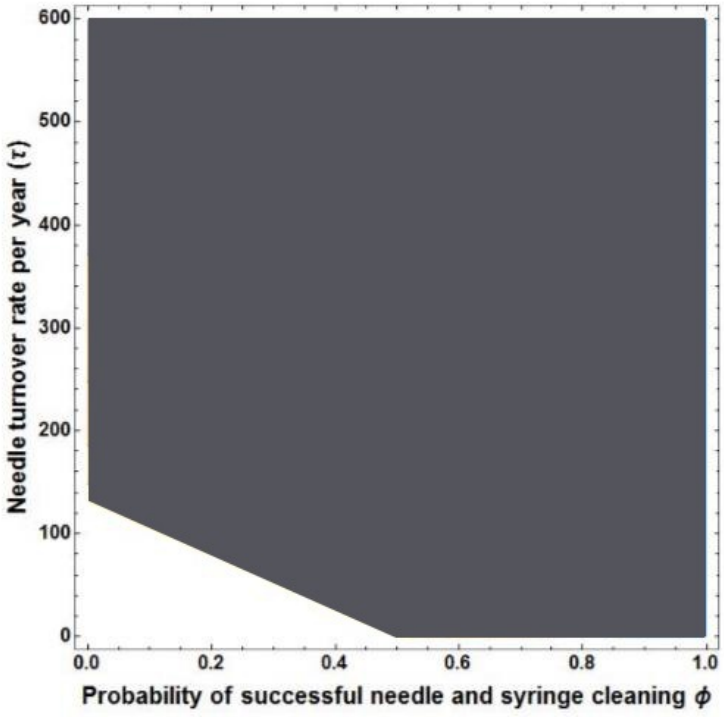

Figure 4.3: Combinations of ϕ and τ that result in $R_0 \leq 1$, grey coloured area.

and that result in HCV elimination in all PWIDs and all needles. These figures clearly show the parameter combinations that will result in $R_0 \leq 1$ in the grey coloured area and the white coloured area means that $R_0 > 1$. Figure 4.3 shows the values of ϕ and τ that are needed to achieve an HCV free population or $R_0 \leq 1$, it is clear from the figure when these parameters lie in the grey coloured area that means $R_0 \leq 1$ otherwise $R_0 > 1$. Similarly, Figure 4.4 indicates the combinations of ψ and τ, the same as before when these parameters lie in the grey coloured area that means $R_0 \leq 1$ otherwise $R_0 > 1$. Moreover, Figure 4.5 indicates the combinations of ψ and ϕ also again as previous parameters when these parameters lie in the grey coloured area that means $R_0 \leq 1$ otherwise $R_0 > 1$.

4.6.4 How the proportion of PWIDs that can spontaneously resolve HCV infection affects model predictions.

During the literature review of parameter values in the simple model, we found that estimating the proportion of PWIDs that spontaneously resolve HCV infection is most difficult since the most of cases are asymptomatic and therefore go undiagnosed. The results of the systematic review into spontaneous viral clearance is $\delta = 26\%$. Therefore,

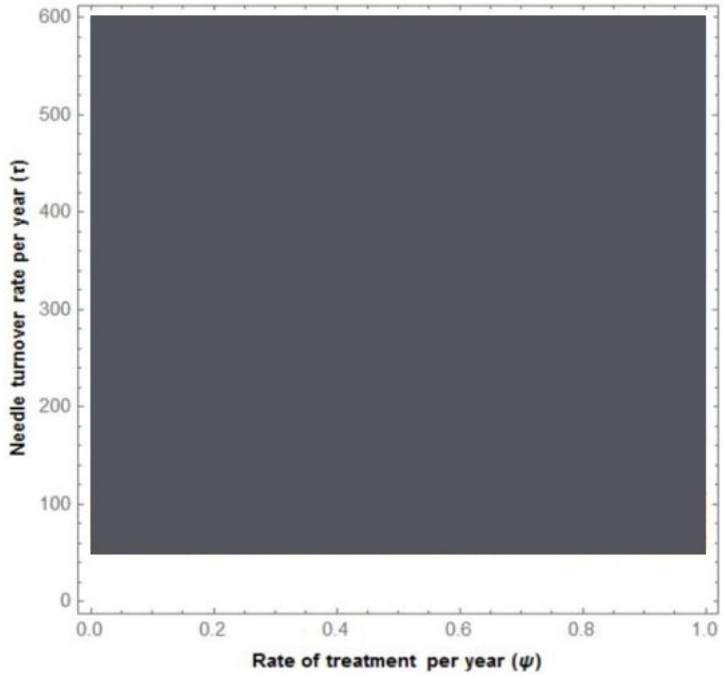

Figure 4.4: Combinations of ψ and τ that result in $R_0 \leq 1$, grey coloured area.

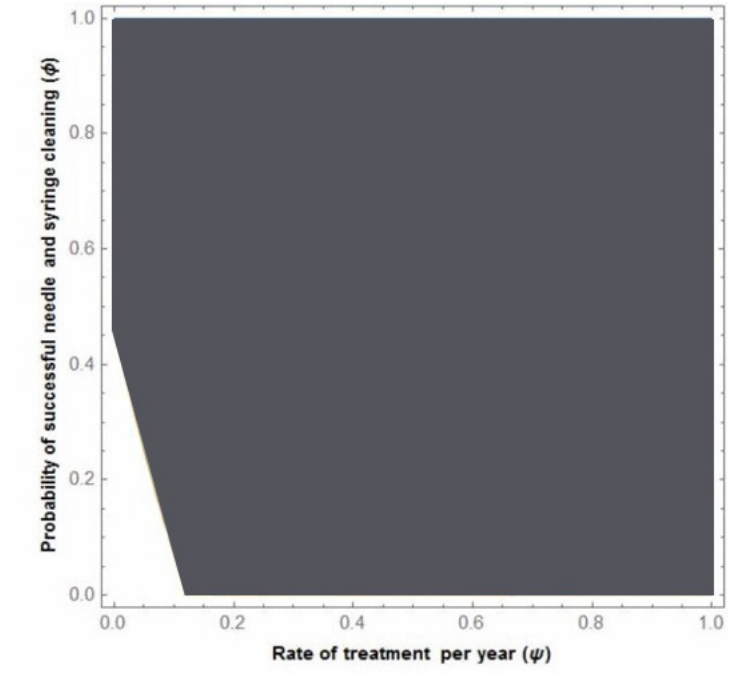

Figure 4.5: Combinations of ψ and ϕ that result in $R_0 \leq 1$, grey coloured area.

δ	Prevalence among sharing PWIDs
0.15	0.95227
0.26	0.95286
0.5	0.95190

Table 4.4: Endemic equilibrium HCV prevalence for sharing PWIDs and needles with $\delta = 0.015, 0.026$ and 0.5.

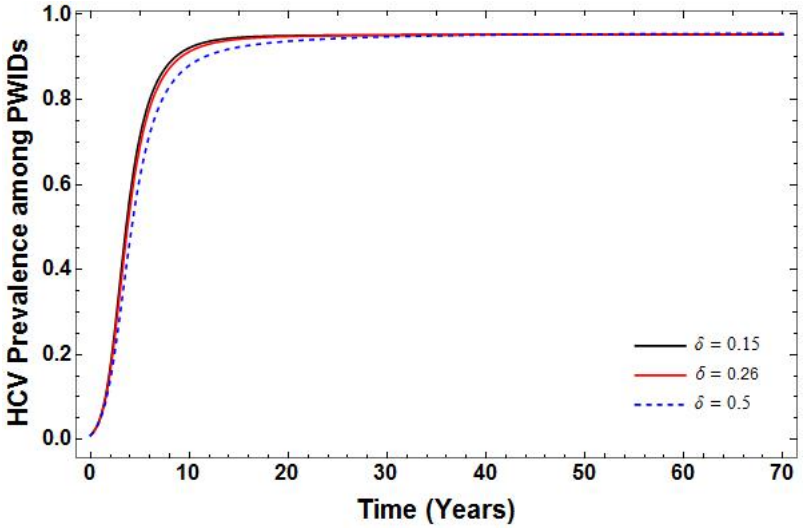

Figure 4.6: HCV prevalence using baseline parameter estimates for 1990-1993.

other researchers have estimated a range of values with Hutchinson et al. (2006a) suggesting 15-40%, Vickerman et al. (2007) suggesting 18-50% and Kamal (2008) suggesting 10-60% before stating that the general rule of thumb is 20%-40%.

In this part we are going to see how these changing assumptions will affect our equilibrium estimates of HCV prevalence and proportion of infectious PWIDs in the population.

Our simulations show that decreasing our suggested δ to 0.15 results in our long term HCV prevalence estimates increasing by only 0.05%. In a similar way, we can see that increasing δ from 0.26 to 0.5 will decrease our long term prevalence estimates by just 0.09%. Therefore, it is clear that there is a slight change in our model behaviour when this parameter is changed. Despite our simple model, we can see in this model the change in behaviour is very small.

α_y	Prevalence among sharing PWIDs
0.0160	0.944422
0.0296	0.956116
0.0432	0.963448

Table 4.5: Endemic equilibrium HCV prevalence estimates for sharing PWIDs and needles with chronic HCV transmission probability of $\alpha_y = 0.0160$, 0.0296 and 0.0432.

4.6.5 The influence of the probability of HCV transmission for chronic infection on model predictions.

We have seen from our literature review that some models of HCV assume that the probability of chronic HCV transmission is equal to the probability of acute HCV transmission. On the other hand other models assume that there is a difference between these two probabilities. In the model of Vickerman et al. (2009) fits were obtained when they did not use the same transmission probabilities as well as when transmission probabilities were assumed to be the same.

In this subsection and the next one we will investigate how these two different assumptions affect our simulations of long term HCV prevalence.

In our next set of simulations (note that we will use the same values of α_y which we estimated for the simple model for purpose of comparison), we will examine the long term prevalence when $\alpha_y = 0.0160$, 0.0296 and 0.0432. Figure 4.7 presents how the model behaviour changes with each parameter estimate. As we expected from previous work in Chapter 3 a lower estimate for α_y similarly to α_y in the simple model will reduce 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 differ under each assumption we summarise the equilibrium values in a table (see Table 4.5). From this table we show that expanding or in other words increasing our estimate of α_y from 0.016 to 0.0432 results in the long term prevalence estimate increasing by 1.9%. If we compare this result with that from the simple model which was 14% then there is a big difference of change of

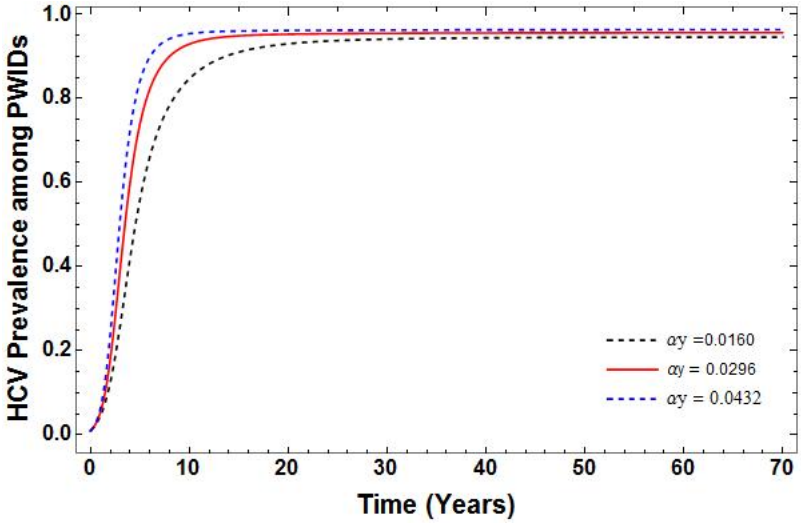

Figure 4.7: HCV prevalence among shared needles $\alpha_y = 0.0160, 0.0296$ and 0.0432.

behaviour of this model with that change in the simple model.

4.6.6 The influence of the probability of HCV transmission for acute infection on model predictions.

While searching the literature for parameter estimates we represented a range of estimates for the probability of acute HCV transmission (see Table 3.1). In the following simulations we examine how the different estimates for this parameter affect the long term estimates of our transmission model.

In our next set of simulations (note that we will use the same values of α_h which we estimated for the simple model for purpose of comparison) we will examine the long term prevalence when $\alpha_h = 0.016$, 0.026, 0.05 and 0.14. Figure 4.8 presents 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 4.6). From this table we show that expanding or in other words increasing our estimate of α_h from 0.016 to 0.05 results in the long term prevalence estimate increasing by 1.7%. If we compare this result with that which we have from the simple model which was 6.7% then it is also a much

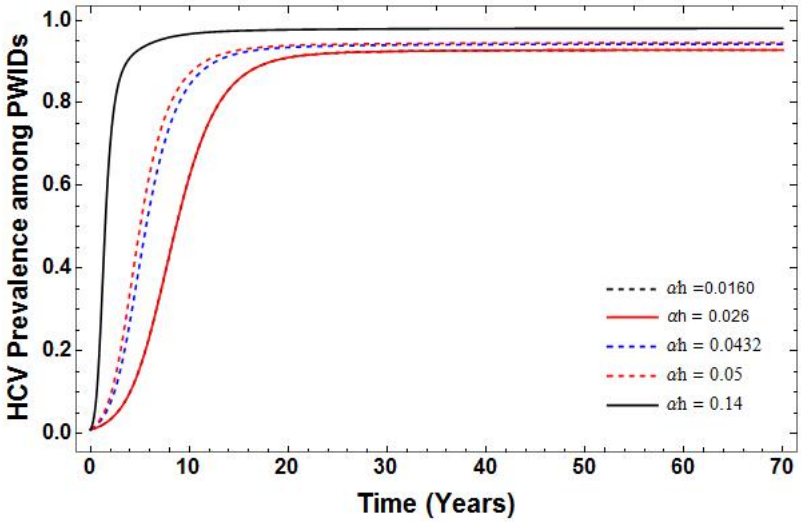

Figure 4.8: HCV prevalence among sharing PWIDs $\alpha_h = 0.0160, 0.026, 0.0432, 0.05$ and 0.14.

α_h	Prevalence among sharing PWIDs
0.016	0.9268
0.026	0.9269
0.0432	0.9413
0.05	0.9446
0.14	0.9797

Table 4.6: Endemic equilibrium HCV prevalence for sharing PWIDs with acute HCV transmission probability of $\alpha_h = 0.016, 0.026, 0.0432, 0.05$ and 0.14.

smaller increase in absolute terms than the corresponding increase for the simple model.

4.7 Comparison between our results and the results of Corson (2011) when we use the Glasgow PWID survey data collected between 1990-1993 and 2008-2009

Again to understand the difference between our model and Corson's model then we need to go back to the previous chapters (Section 3.1), our model is more pessimistic than Corson's model because of we have based our model on the assumption of Lewis and Greenhalgh (2001) and Corson's model is based on the assumption of Greenhalgh and Lewis (2000). Also we have introduced the rate of treatment ψ in our model which was not considered in Corson's model. Hence again we expect that disease will spread faster in our model than Corson's model.

Note that our two values of R_0 for the period 1990-1993 with $\psi = 0$ per year and $\psi = 0.1$ per year both of them are bigger than the one obtained for Corson's model (we have summarised these results in Table 4.7) even though we have introduced treatment of infected PWIDs into the model. This is because we have changed the PWID needle interaction assumptions from the optimistic PWID needle interaction assumptions of Corson (2011) and Corson et al. (2013) to the pessimistic PWID needle interaction assumptions of Lewis and Greenhalgh (2001). Changing the PWID needle interaction assumptions without treatment is decreased R_0 from 10.474 (when $\psi = 0$ per year) to 6.177 when we have introduced treatment ($\psi = 0.1$ per year). A similar scenario happened when we used the data survey for the period 2008-2009 which is R_0 decreased from 0.0492 to 0.0275 when we consider treatment.

4.8 Conclusion

In this chapter we have separated the PWID population according to infection status, this modified model further separates the participant PWIDs into two groups. These two group numbers vary depending on whether the individuals participating in the research

R_0	1990-1993	2008-2009
Our results with $\psi = 0$ per year	10.474	0.049
Our results with $\psi = 0.1$ per year	6.177	0.027
Corson (2011) results	3.598	0.009

Table 4.7: Comparison between our R_0 results and Corson's results for two periods of time 1990-1993 and 2008-2009.

have a short (naive) or long (experienced) injecting career. 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 PWIDs. If $R_0 > 1$ we have shown that there is a endemic equilibrium. Also we have tried to prove the uniqueness of endemic equilibria analytically and numerically (by using Wolfram Mathematica) but I have not found any results because it is difficult and very complicated and it is still the open question and may be can prove in future, in Corson's model the uniqueness has been proved analytically but the same method does not carry over to our model.

Our model is different than the model discussed in Corson (2011) and Corson et al. (2013) because of the PWID needle interactions and the ψ term. Particularly the equilibrium analysis and simulation results. Also we have used the basic parameter estimates given in Corson (2011) but the model is different and there is treatment which leads to a differerent and more complex approach to the mathematical analysis than studies in Corson (2011) and Corson et al. (2013). Moreover we have examined combinations of the control parameters ϕ, ψ and τ that give $R_0 \leq 1$ which was not done for this model in Corson (2011) and Corson et al. (2013) (additionally this could not have been done because Corson's model did not consider ψ). Also we have examined the sensitivity of the model predictions to parameter estimates which was not done for this model in Corson (2011) and Corson et al. (2013).

Lastly, in this chapter we analysed the behaviour of our model over time using the numerical simulation package Wolfram Mathematica version 11.1. 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.

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 PWIDs and needles. Again by using the package Wolfram Mathematica version 11.1 we further varied all three control parameters (ψ, ϕ and τ) simultaneously to find the combination which gives $R_0 \leq 1$. Lastly we have compared our R_0 results with those of Corson (2011) when we have introduced treatment and without treatment.

Chapter 5

A Simple Pessimistic Model for the Effects of Heterogeneity on the Spread of HCV amongst PWIDs

It is common knowledge that heterogeneity in a population may enhance or inhibit the transmission of contagions thereby affecting the effectiveness of strategies to control infections (Anderson and May (1992)). Heterogeneity is the main factor that complicates a model's structure, both in individuals on infection from the outside population and in pathogens as well. Active research on infectious disease epidemiology focuses on a variety of potentially important problems. It is therefore important to accommodate individual heterogeneity in statistical and mathematical models in disease research. These models involve specifying contact rates between individuals (Farrington et al. (2013)).

Heterogeneity in a population can play a vital role in the outbreak of an epidemic. The heterogenous population is divided into subgroups with each group having similar characteristics in its members. The subgroups are based on factors, such as amount of vaccination, infectious period, route of transmission, latent period, social, geographic, age, cultural and economic factors (Al-Fwzan (2015)). Heterogeneity in disease transmission leans heavily on the social behaviour of the population at risk for the disease. Hence, the question :'Who mixes with whom?' (Hethcote

(1996)). Many epidemiological models are formulated with multiple groups with defined contact matrices for the interaction of individuals within the groups. Examples of such models are those by Lajmanovich and Yorke (1976),Nold (1980),Dushoff and Levin (1995) and Greenhalgh (1996).

The formulation of a deterministic mathematical model regarding the impact of heterogeneity on HCV dissemination amongst PWIDs and shooting galleries is the focus of the current chapter. We start off by discussing previous work on the effect of heterogeneity on the spread of HCV and HIV/AIDS amongst PWIDs. Next the chapter proceeds by addressing a series of hypotheses considered to underpin the differential equation system characterising HCV dissemination.

An article on heterogeneity in disease modelling is discussed by Nold (1980) with a consideration of a heterogeneously mixing epidemic model as a factor in the application to gonorrhea. This is a pioneering article in mathematical modelling reflecting heterogeneity in the spread of a disease. The author has provided a link between the basic reproduction number R_0 within a heterogeneously mixing population and the spectral radius of a given operator to provide a firmer mathematical basis for the results. The basic reproduction number is given as the spectral radius of a given matrix. The disease dies out if this spectral radius is less than one but takes off if the spectral radius exceeds one.

A mathematical model was developed by Greenhalgh (1996) to study how HIV and AIDS are spread amongst PWIDs in shooting galleries. Additionally the researcher studies how the spread of HIV and AIDS in a population of PWIDs was changed by heterogeneity effects. Greenhalgh reflected on the variability in shooting gallery visiting rate exhibited when PWIDs visit shooting galleries, choice of shooting galleries and whether the needles are cleaned before use.

However Greenhalgh (1996) was concerned with a heterogeneously mixing model through a mathematical analysis that reflected on the transmission of HIV within the population of intraveneously injecting PWIDs. Al-Fwzan (2015) studied a similar model for heterogeneity in the spread of HCV amongst a population of PWIDs. Al-Fwzan was working with the 'optimistic' needle-PWID assumption similar to that of Corson et al. (2012) and Greenhalgh and Lewis (2000). Here a needle automatically

adapts the infectious state of the last PWID to use it. We shall study a similar model to Al-Fwzan (2015) but we shall be working with two assumptions similar to the needle-PWID interaction assumptions of Lewis and Greenhalgh (2001a). Here each time that a needle is used it adopts the most infectious of its previous state and the infectious state of the last PWID to use it. Additionally unlike Al-Fwzan (2015) we take into account the treatment of chronically infected PWIDs with antiviral therapy.

In the following part the model description is outlined and the model equations are derived afterwards. We have followed hypotheses similar to those of Al-Fwzan (2015) except that in Al-Fwzan's model the PWID-needle interaction assumptions are different and there is no treatment of infected PWIDs. Then we derive our new model equations after that an expression for the basic reproduction number of the model, R_0 was derived. Next we show that if $R_0 \leq 1$ the system of differential equations has a unique solution where the disease has died out in each group of PWIDs and each shooting gallery. We show that this unique endemic equilibrium is globally asymptotically stable if $R_0 < 1$. The numeric solution of the ordinary differential equation system of our models was made by the use of Wolfram Mathematica software.

5.1 Model description

We create a deterministic mathematical model of the prevalence of HCV amongst PWIDs in shooting galleries, basing our model on the simple model that we have discussed in Chapter 2. This model relies on the assumption that is used in Al-Fwzan (2015). Therefore the parameters ϕ_{ij}, λ_i, τ_j, μ, α_h, α_y, σ, δ, α, P_{ij} and m_j are still similar to the definition in Al-Fwzan's model (see Table 1.4). Also, we assume that the per capita rate at which chronically infected PWIDs are successfully treated is ψ.

Again as assumed in Al-Fwzan (2015) the modified model to be applied here also allows for dividing the PWIDs population of type i into x_i, x_{1i}, h_{1i}, h_{2i}, y_i and z_i which represent respectively to those not previously infected, those previously

infected, those in the acute h_1 stage of HCV infection, those in the acute h_2 stage of HCV infection, those who have progressed to the chronic stage of HCV infection and those immune to HCV reinfection.

Similarly, the shooting galleries are divided into q groups labeled $j = 1, 2, ...q$. The difference here between our model and Al-Fwzan's model on the way that a type i PWID can be infected PWID so the infectivity of each needle is determined by the highest level of infectiousness that it has previously come into contact with. For example, suppose that an acute stage h_1 infectious needle in shooting gallery j is used by a PWID in the chronic y stage of infection. The needle will remain in the acute h_1 infectious state. On the other hand a needle in the chronic y state of infection used by a PWID in the acute h_1 infectious stage will be left in the acute h_1 infectious state. This assumption agrees with that made by Lewis and Greenhalgh (2001a) and makes this model pessimistic compared to other possible assumptions and so we expect that it could be used to find a lower bound for the fraction of PWIDs and needles infected with HCV.

5.2 Dynamic equations

We are now going to derive the differential equations which give the spread of HCV among PWIDs where PWIDs move through the different stages of HCV infection represented in the previous subsection and HCV infection is caused by sharing the three types of infectious needle which is again described in the previous subsection.

Let $\pi_{xi}(t)$, $\pi_{x_1i}(t)$, $\pi_{h_1i}(t)$, $\pi_{h_2i}(t)$, $\pi_{yi}(t)$ and $\pi_{zi}(t)$ denote the fraction of PWIDs out of PWIDs in group i respectively in the x_i-susceptible, x_{1i}-susceptible, acute h_{1i}, acute h_{2i}, chronic y_i and immune z_i classes at time t. Note that in our model we consider the rate of treatment ψ which was not included in the model of Al-Fwzan (2015) then we have new different equations for the x_i-susceptible and chronic y_i classes. The other PWID equations for the other classes are still the same. In a similar way, $\beta_{h_1j}(t)$, $\beta_{h_2j}(t)$ and $\beta_{yj}(t)$ respectively denote the fractions of HCV infectious needles at time t in shooting gallery j that were last used by an infected PWID in infectious state h_1, h_2 and y respectively. Also we shall discuss two different

possible sets of assumptions than discussed by Al-Fwzan (2015) for how stage h_1, stage h_2 and stage y infectious needles and stage h_1, stage h_2 and stage y infectious PWIDs interact. Note that in this model, the parameter μ is both the per capita birth rate and the per capita death rate for all PWIDs.

Using a similar way to the way that we derived our differential equations in Chapter 2 then we can derive the system of governing equations that describe the spread of HCV among PWIDs which is given by:

For $i = 1, 2, \ldots p$, and $j = 1, 2, \ldots q$.

$$\frac{d\pi_{x_i}}{dt} = \mu - \mu\pi_{x_i} - \pi_{x_i}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}} + \beta_{h_{2j}}) + \alpha_y\beta_{y_j}\big) + \psi\pi_{y_i}, \quad (5.2.1)$$

$$\frac{d\pi_{x_{1i}}}{dt} = \sigma(1-\alpha)\pi_{h_{2i}} - \mu\pi_{x_{1i}} - \pi_{x_{1i}}\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}} + \beta_{h_{2j}}) \quad (5.2.2)$$

$$+\alpha_y\beta_{y_j}\big),$$

$$\frac{d\pi_{h_{1i}}}{dt} = \sum_{j=1}^{q}(1-\delta)(\pi_{x_i} + \pi_{x_{1i}})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}} + \beta_{h_{2j}}) + \alpha_y\beta_{y_j}\big) \quad (5.2.3)$$

$$-(\mu+\sigma)\pi_{h_{1i}},$$

$$\frac{d\pi_{h_{2i}}}{dt} = \sum_{j=1}^{q}\delta(\pi_{x_i} + \pi_{x_{1i}})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_h(\beta_{h_{1j}} + \beta_{h_{2j}}) + \alpha_y\beta_{y_j}\big) \quad (5.2.4)$$

$$-(\mu+\sigma)\pi_{h_{2i}},$$

$$\frac{d\pi_{y_i}}{dt} = \sigma\pi_{h_{1i}} - \mu\pi_{y_i} - \psi\pi_{y_i}, \quad (5.2.5)$$

$$\frac{d\pi_{z_i}}{dt} = \sigma\alpha\pi_{h_{2i}} - \mu\pi_{z_i}. \quad (5.2.6)$$

Under Assumption 1 for needles

$$\frac{d\beta_{h_{1j}}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}}(1-\beta_{h_{1j}}) - \beta_{h_{1j}}\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij}(1-\pi_{h_{1i}}) - \tau_j\beta_{h_{1j}}, \quad (5.2.7)$$

$$\frac{d\beta_{h_{2j}}}{dt} = \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}}(1-\beta_{h_{1j}}-\beta_{h_{2j}}) + \beta_{h_{1j}}\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij}\pi_{h_{2i}} - \beta_{h_{2j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}} \quad (5.2.8)$$

$$-\beta_{h_{2j}}\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij}(1-\pi_{h_{1i}}-\pi_{h_{2i}}) - \tau_j\beta_{h_{2j}}.$$

Under Assumption 2 for needles

$$\frac{d\beta_{h_{1j}}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_{1i}}(1-\beta_{h_{1j}}) - \beta_{h_{1j}} \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_{2i}} \tag{5.2.9}$$
$$-\beta_{h_{1j}} \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi_{h_{1i}}-\pi_{h_{2i}}) - \tau_j\beta_{h_{1j}}.$$
$$\frac{d\beta_{h_{2j}}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_{2i}}(1-\beta_{h_{2j}}) - \beta_{h_{2j}} \sum_{i=1}^{p} \Lambda_{ij}\pi_{h_{1i}} \tag{5.2.10}$$
$$-\beta_{h_{2j}} \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi_{h_{1i}}-\pi_{h_{2i}}) - \tau_j\beta_{h_{2j}}.$$

For both Assumptions we have that

$$\frac{d\beta_{y_j}}{dt} = \sum_{i=1}^{p} \Lambda_{ij}\pi_{y_i}(1-\beta_{h_{1j}}-\beta_{h_{2j}}-\beta_{y_j}) + (\beta_{h_{1j}}+\beta_{h_{2j}}) \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}\pi_{y_i} \tag{5.2.11}$$
$$-\beta_{y_j} \sum_{i=1}^{p} \Lambda_{ij}(\pi_{h_{1i}}+\pi_{h_{2i}}) - \beta_{y_j} \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi_{h_{1i}}-\pi_{h_{2i}}-\pi_{y_i}) - \tau_j\beta_{y_j},$$

with suitable initial conditions: $\pi_{x_i}(0)$, $\pi_{x_{1i}}(0)$, $\pi_{h_{1i}}(0)$, $\pi_{h_{2i}}(0)$, $\pi_{y_i}(0)$, $\pi_{z_i}(0)$ for $i = 1, 2, \ldots p$ and $\beta_{h_{1j}}(0)$, $\beta_{h_{2j}}(0)$, $\beta_{y_j}(0) \geq 0$ with $\sum_{b\in\{h_{1j},h_{2j},yj\}} \beta_{bj}(0) < 1$ for $j = 1, 2, \ldots q$.

5.3 Difference to Al-Fwzan's model

The model of Al-Fwzan (2015) assumes that after use by an infected PWID each needle takes on the infectious state of the last PWID to use it but in our model we have used two sets of alternative assumptions which assume that the infectious state of the needle can only increase during its lifetime. Also we are following the structure of the corresponding chapter in Al-Fwzan's thesis because we want to compare the results between the model of Al-Fwzan (2015) and the two sets of models discussed in this chapter. Moreover, the difference between the model discussed in Al-Fwzan (2015) and the two sets of models discussed in this thesis is similar to the difference between the models for the spread of HIV of Greenhalgh and Lewis (2000) who use an 'optimistic assumption' similar to Al-Fwzan's model, and the model of Lewis and Greenhalgh (2001) who use a 'pessimistic' assumption similar to our model. Therefore the PWID-needle interactions are more complicated in our models than those

in Al-Fwzan (2015). As well as the different PWID needle interaction assumptions in our model PWIDs can also be treated at per capita rate ψ.

5.4 The basic reproduction number R_0

This derivation is similar to that of Section 2.3 of Al-Fwzan (2015) although it differs in the ψ term and the PWID needle interaction terms. Therefore as with previous simple model in Chapter 2 we need to derive an expression for the basic reproduction number for the model defined by equations (5.2.1)-(5.2.11).

Again consider a single newly infectious PWID in group i entering a totally susceptible population of PWIDs and needles at equilibrium. Using the methods outlined in Section 2.2 of this thesis and Section 3.2 of Al-Fwzan (2015) then we have that the single PWID in group i will infect on average

$$\frac{\lambda_i P_{ij}(1-\delta)}{\mu+\sigma}$$

acute h_{1j} infectious needles,

$$\frac{\lambda_i P_{ij}\delta}{\mu+\sigma}$$

acute h_{2j} infectious needles and

$$\frac{\lambda_i P_{ij}\sigma(1-\delta)}{(\mu+\psi)(\mu+\sigma)}$$

chronic y_j infectious needles, in shooting gallery j.

By again dealing with each type of infectious needle which is used by uninfected PWIDs of different groups $k = 1, 2, ...p$ and using the same method and notation in Section 2.2 then we have that

$$E_{h_{1j}} = \frac{\alpha_h \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j} + \frac{\sum_{l=1}^{p}\Lambda_{lj}(1-\phi_{lj})}{\sum_{l=1}^{p}\Lambda_{lj}+\tau_j} E_{h_{1j}} \tag{5.4.12}$$

Hence solving (5.4.12) for $E_{h_{1j}}$ gives

$$E_{h_{1j}} = \frac{\alpha_h \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j} \qquad \text{PWIDs in group } k, \tag{5.4.13}$$

Therefore, we use a similar argument to derive the expected number of PWIDs that are infected by acute h_{2j} and chronic y_j needles in both assumptions of needles until they are uninfectious. These are

$$E_{h_{2j}} = \frac{\alpha_h \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j} \qquad \text{PWIDs in group } k, \tag{5.4.14}$$

and

$$E_{y_j} = \frac{\alpha_y \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j} \qquad \text{PWIDs in group } k. \tag{5.4.15}$$

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

$$\begin{aligned} Q_{ik} &= \sum_{j=1}^{q} \left(\frac{\lambda_i P_{ij}(1-\delta)}{\mu+\sigma} \cdot \frac{\alpha_h \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j} \right. \\ &\quad + \frac{\lambda_i P_{ij}\delta}{\mu+\sigma} \cdot \frac{\alpha_h \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j} \\ &\quad \left. + \frac{\lambda_i P_{ij}\sigma(1-\delta)}{(\mu+\psi)(\mu+\sigma)} \cdot \frac{\alpha_y \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j} \right), \\ &= \xi \sum_{j=1}^{q} \frac{\lambda_i P_{ij} \Lambda_{kj}(1-\phi_{kj})}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j}, \end{aligned} \tag{5.4.16}$$

where $\xi = (\alpha_y\sigma(1-\delta) + \alpha_h(\mu+\psi))/(\mu+\psi)(\mu+\sigma)$. Hence, define R_0 as the spectral radius of $\boldsymbol{Q}$ as in Al-Fwzan (2015) and Greenhalgh (1996) therefore the basic reproduction number R_0 is given by:

$$\rho(\boldsymbol{Q}) = \max_{1 \le i \le p} |\lambda_i| \tag{5.4.17}$$

where $\lambda_1, \lambda_2, ..., \lambda_p$ are the eigenvalues of $\boldsymbol{Q}$.

Thus, we conclude that R_0 is the same for Assumption 1 and Assumption 2. Moreover it is different than R_0 in Al-Fwzan (2015) because of the ψ terms and also the factor $(\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j)$ in the denominator. If we set $\psi = 0$ per year and replace the terms $(\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j)$ in the denominator by $(\sum_{l=1}^{p} \Lambda_{lj} + \tau_j)$ then we get the matrix $\mathbf{Q}$ discussed in Chapter 2 of Al-Fwzan (2015). Al-Fwzan (2015) showed that R_0 could be expressed as the largest eigenvalue of a matrix $\hat{Q}_{jr}$ where $\hat{Q}_{jr} = \xi \sum_{k=1}^{p} \Lambda_{kj}(1-\phi_{kj})\lambda_k P_{kr}/(\sum_{l=1}^{p} \Lambda_{lj} + \tau_j)$ derived from a matrix $\boldsymbol{M}$

corresponding to the expected number of needles resulting from a single infectious needle entering the disease-free population at equilibrium and we expect the same corresponding result to be true for our model if we replace ξ by its new definition and $(\sum_{l=1}^{p} \Lambda_{lj} + \tau_j)$ in the denominator of the terms in the sum of the right hand side of $\hat{Q}$ by $(\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j)$.

Epidemiological models accord great significance to R_0 because it is a universal concept applicable to almost if not all epidemic models that usually gives a single key threshold parameter that determines the overall behaviour of the model. In the above part we described a completely general model for PWIDs visiting shooting galleries where PWIDs had a completely general choice of shooting galleries to visit.

5.5 Analytical results

The creation of a deterministic model of heterogeneous populations requires identification of the circumstances for equilibria and local and global stability and determination of how those circumstances (epidemic outbreak and subsidence thresholds) are correlated. The way in which the proposed transmission model behaves is the focus of the current part, with emphasis on the circumstances in which HCV can be eradicated. The type of equilibrium solutions is established based on an equilibrium and stability analysis, in relation to which the basic reproduction number R_0 is a crucial parameter. Furthermore, it will be demonstrated that a zero solution representing a disease-free equilibrium exists and is a possibility in all cases. Moreover, the disease-free equilibrium will be globally asymptotically stable if the value of R_0 is 1 or less than 1, signifying eventual disease elimination in all PWIDs and shooting galleries.

If we use the PWID-needle interaction assumptions of Corson's model and $\psi = 0$ the next theorem translates to Theorem 3.1.1 of Al-Fwzan (2015) adapted to our model.

Theorem 5.5.1. *In either system (5.2.1)-(5.2.8) and (5.2.11) or (5.2.1)-(5.2.6) and (5.2.9)-(5.2.11), if $R_0 \leq 1$ then the system has a unique equilibrium solution where the disease has died out in each group of PWIDs and in each shooting gallery.*

Proof. Note that the idea of the proof is similar to that of Al-Fwzan (2015) but the main difference is the needle equations. There is also the needle exchange rate ψ. Several stages are used to prove the theorem. First, needles and PWIDs equilibrium proportions are denoted as β^*_{lj} and π^*_{si} where $l = h_1, h_2, y$ and $s = x_1, h_1, h_2, y, z$ respectively. Disease-free equilibrium existence is denoted with $\pi^*_{xi} = 1$, $\pi^*_{si} = 0$ and $\beta^*_{lj} = 0$. We need to show that there is no other equilibrium solution. From the equilibrium versions of equations (5.2.7)-(5.2.11), we have the following:

For Assumption 1 for needles,

$$\beta^*_{h_{1j}} = \frac{\sum_{i=1}^{p} \Lambda_{ij}\pi^*_{h_{1i}}}{\sum_{i=1}^{p} \Lambda_{ij}\pi^*_{h_{1i}} + \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi^*_{h_{1i}}) + \tau_j}, \tag{5.5.18}$$

$$\beta^*_{h_{2j}} = \frac{\sum_{i=1}^{p} \Lambda_{ij}\pi^*_{h_{2i}}(1-\beta^*_{h_{1j}}) + \beta^*_{h_{1j}}\sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}\pi^*_{h_{2i}}}{\sum_{i=1}^{p} \Lambda_{ij}(\pi^*_{h_{1i}} + \pi^*_{h_{2i}}) + \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi^*_{h_{1i}} - \pi^*_{h_{2i}}) + \tau_j}. \tag{5.5.19}$$

For Assumption 2 for needles,

$$\beta^*_{h_{1j}} = \frac{\sum_{i=1}^{p} \Lambda_{ij}\pi^*_{h_{1i}}}{\sum_{i=1}^{p} \Lambda_{ij}(\pi^*_{h_{1i}} + \pi^*_{h_{2i}}) + \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi^*_{h_{1i}} - \pi^*_{h_{2i}}) + \tau_j}, \tag{5.5.20}$$

$$\beta^*_{h_{2j}} = \frac{\sum_{i=1}^{p} \Lambda_{ij}\pi^*_{h_{2i}}}{\sum_{i=1}^{p} \Lambda_{ij}(\pi^*_{h_{1i}} + \pi^*_{h_{2i}}) + \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi^*_{h_{1i}} - \pi^*_{h_{2i}}) + \tau_j}. \tag{5.5.21}$$

For both assumptions,

$$\beta^*_{y_j} = \frac{\sum_{i=1}^{p} \Lambda_{ij}\pi^*_{y_i}(1-\beta^*_{h_{1j}} - \beta^*_{h_{2j}}) + (\beta^*_{h_{1j}} + \beta^*_{h_{2j}})\sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}\pi^*_{y_i}}{\sum_{i=1}^{p} \Lambda_{ij}(\pi^*_{h_{1i}} + \pi^*_{h_{2i}} + \pi^*_{y_i}) + \sum_{i=1}^{p} \Lambda_{ij}\phi_{ij}(1-\pi^*_{h_{1i}} - \pi^*_{h_{2i}} - \pi^*_{y_i}) + \tau_j}. \tag{5.5.22}$$

From equation (5.2.3) we have that: $\pi^*_{h_1 i} = (1-\delta)K_i$ such that:

$$K_i = \frac{1}{\mu+\sigma}\sum_{j=1}^{q}(\pi^*_{x_i} + \pi^*_{x_{1i}})\lambda_i P_{ij}(1-\phi_{ij})(\alpha_h(\beta^*_{h_{1j}} + \beta^*_{h_{2j}}) + \alpha_y\beta^*_{y_j}).$$

Also, from equations (5.2.4), (5.2.5) and (5.2.6) we have that:

$$\begin{aligned}
\pi^*_{h_{2i}} &= \delta K_i,\\
\pi^*_{y_i} &= \frac{\sigma(1-\delta)K_i}{\mu+\psi},\\
\pi^*_{z_i} &= \frac{\sigma\alpha\delta K_i}{\mu}.
\end{aligned}$$

Under Assumption 1 for needles,

$$\beta^*_{h_{1j}} = \frac{\sum_{i=1}^p \Lambda_{ij}(1-\delta)K_i}{\sum_{i=1}^p \Lambda_{ij}(1-\delta)K_i + \sum_{i=1}^p \Lambda_{ij}\phi_{ij}\big(1-(1-\delta)K_i\big) + \tau_j},$$
$$\beta^*_{h_{2j}} = \frac{\big(\sum_{i=1}^p \Lambda_{ij}(1-\beta^*_{h_{1j}}) + \beta^*_{h_{1j}}\sum_{i=1}^p \Lambda_{ij}\phi_{ij}\big)\delta K_i}{\sum_{i=1}^p \Lambda_{ij}K_i + \sum_{i=1}^p \Lambda_{ij}\phi_{ij}(1-K_i) + \tau_j},$$

Under Assumption 2 for needles,

$$\beta^*_{h_{1j}} = \frac{\sum_{i=1}^p \Lambda_{ij}(1-\delta)K_i}{\sum_{i=1}^p \Lambda_{ij}K_i + \sum_{i=1}^p \Lambda_{ij}\phi_{ij}(1-K_i) + \tau_j},$$
$$\beta^*_{h_{2j}} = \frac{\sum_{i=1}^p \Lambda_{ij}\delta K_i}{\sum_{i=1}^p \Lambda_{ij}K_i + \sum_{i=1}^p \Lambda_{ij}\phi_{ij}(1-K_i) + \tau_j}.$$

For both assumptions

$$\beta^*_{y_j} = \frac{\sum_{i=1}^p \Lambda_{ij}\big(\frac{\sigma(1-\delta)K_i}{(\mu+\psi)}\big)(1-\beta^*_{h_{1j}}-\beta^*_{h_{2j}}) + (\beta^*_{h_{1j}}+\beta^*_{h_{2j}})\sum_{i=1}^p \Lambda_{ij}\phi_{ij}\big(\frac{\sigma(1-\delta)K_i}{(\mu+\psi)}\big)}{\sum_{i=1}^p \Lambda_{ij}\left(K_i + \big(\frac{\sigma(1-\delta)K_i}{\mu+\psi}\big)\right) + \sum_{i=1}^p \Lambda_{ij}\phi_{ij}\left(1-K_i - \big(\frac{\sigma(1-\delta)K_i}{\mu+\psi}\big)\right) + \tau_j}. \tag{5.5.23}$$

Writing $\pi^*_{h_i} = \pi^*_{h_{1i}} + \pi^*_{h_{2i}} = K_i$ for both assumptions of needles we have that:

$$\beta^*_{h_{1j}} + \beta^*_{h_{2j}} \leq \frac{\sum_{k=1}^p \Lambda_{kj}\pi^*_{h_k}}{\sum_{k=1}^p \Lambda_{kj}\phi_{kj} + \tau_j},$$
$$\beta^*_{h_{1j}} + \beta^*_{h_{2j}} + \beta^*_{y_j} \leq \frac{\sum_{k=1}^p \Lambda_{kj}(\pi^*_{h_k} + \pi^*_{y_k})}{\sum_{k=1}^p \Lambda_{kj}\phi_{kj} + \tau_j}.$$

These inequalities follow from solving the equilibrium versions of equations $\frac{d}{dt}(\beta_{h_1} + \beta_{h_2})$ and $\frac{d}{dt}(\beta_{h_1} + \beta_{h_2} + \beta_y)$ as in Chapter 2 or directly using 5.5.18-5.5.22

We get a bound for π^*_{hi} as the following (similar to Al-Fwzan (2015)):

$$\begin{aligned}
\pi^*_{h_i} &= \pi^*_{h_{1i}} + \pi^*_{h_{2i}} = (1-\delta)K_i + \delta K_i, \\
&= \frac{1}{\mu+\sigma}\sum_{j=1}^{q}(\pi^*_{x_i} + \pi^*_{x_{1i}})\lambda_i P_{ij}(1-\phi_{ij})\big(\alpha_y(\beta^*_{h_{1j}} + \beta^*_{h_{2j}} + \beta^*_{y_j}) \\
&\qquad + (\alpha_h - \alpha_y)(\beta^*_{h_{1j}} + \beta^*_{h_{2j}})\big), \\
&\leq \frac{1}{\mu+\sigma}\sum_{j=1}^{q}(1 - \pi^*_{h_{1i}} - \pi^*_{h_{2i}} - \pi^*_{y_i} - \pi^*_{z_i})\lambda_i P_{ij}(1-\phi_{ij}) \\
&\qquad \times \left(\alpha_y\left(\frac{\sum_{k=1}^{p}\Lambda_{kj}(\pi^*_{h_k} + \pi^*_{y_k})}{\sum_{k=1}^{p}\Lambda_{kj}\phi_{kj} + \tau_j}\right) + (\alpha_h - \alpha_y)\left(\frac{\sum_{k=1}^{p}\Lambda_{kj}\pi^*_{h_k}}{\sum_{k=1}^{p}\Lambda_{kj}\phi_{kj} + \tau_j}\right)\right), \\
&= \frac{1}{\mu+\sigma}\left(1 - \pi^*_{hi}\left(1 + \frac{\sigma}{\mu+\psi}(1-\delta) + \frac{\sigma}{\mu}\delta\alpha\right)\right) \\
&\qquad \times \sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\frac{\sum_{k=1}^{p}\Lambda_{kj}\pi^*_{h_k}}{\sum_{k=1}^{p}\Lambda_{kj}\phi_{kj} + \tau_j}\left(\alpha_h + \alpha_y\frac{\sigma}{\mu+\psi}(1-\delta)\right), \\
&\leq \sum_{k=1}^{p} Q^*_{ik}\pi^*_{hk}. \qquad (5.5.24)
\end{aligned}$$

Here

$$Q^*_{ik} = \sum_{j=1}^{q}\frac{\xi\lambda_i P_{ij}\Lambda_{kj}(1-\phi_{ij})}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj} + \tau_j}. \qquad (5.5.25)$$

We denote the matrix with elements Q^*_{ik} by $\boldsymbol{Q}^*$.

Lemma 5.5.2. *The matrix Q^*_{ik} where*

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

and matrix $\boldsymbol{Q}^T$ where

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

have the same eigenvalues, see equation (5.5.25).

Proof. The idea of Lemma 3.1.2 within Al-Fwzan (2015) gives us an overview of the prevailing proof where we write

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

Hence,

$$Q_{ik}^{T} = \sum_{j=1}^{q} \frac{\xi \lambda_k P_{kj} \Lambda_{ij} (1 - \phi_{ij})}{b_j},$$

so arguing as in Lemma 3.1.2 of Al-Fwzan (2015) with a_j replaced by b_j then we have

$$Q_{ik}^{T} = Q_{ik}^{*} \frac{n_i}{n_k}.$$

Therefore as results we have that $(e_1, e_2, \ldots, e_p)$ is a left eigenvector of the matrix Q_{ik}^{T} and $(n_1 e_1, n_2 e_2, \ldots, n_p e_p)$ is a left eigenvector of the matrix Q_{ik}^{*}. Therefore our proof is completed. □

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

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

and therefore transmission of the infection forwards by every group of PWIDs is possible.

Again we are following the similar idea which was used in Al-Fwzan (2015) then the proof of the Theorem 5.5.1 needs completion when $R_0 \leq 1$. We need to show that there is only the zero equilibrium if R_0 is less than or equal to unity. A contradiction method can be used to prove this. Suppose there is another solution with some $\pi_{hi_0}^{*} = K_{i_0} > 0$. Then from the equilibrium solution (5.5.23) we deduce that each of

$$\pi_{h_1 i_0}^{*}, \quad \pi_{h_2 i_0}^{*}, \quad \pi_{y_{i_0}}^{*}, \quad \text{and} \quad \pi_{z_{i_0}}^{*},$$

is strictly deduced as positive. Reflecting on both equivalent versions of equations (5.2.1) and (5.2.2), it is clear that $\pi_{xi_0}^{*} > 0$ and $\pi_{x_1 i_0}^{*} > 0$. Additionally, at any $j = 1, 2, \ldots, q$ as per the equilibrium equation (5.5.23), we deduce that

$$\beta_{h_1 j}^{*}, \quad \beta_{h_2 j}^{*}, \quad \text{and} \quad \beta_{y_j}^{*},$$

are strictly greater than zero.

The proof of Theorem 1.5.1 now follows as the proof of Theorem 3.1.1 of Al-

Fwzan (2015) to deduce that $K_i = 0$ for each i. The result follows as in Al-Fwzan (2015) except that there are some minor differences in the PWID and needle equations so the details are not exactly the same but the idea is the same. So if i is another group of PWIDs then considering the equilibrium versions of (5.2.1), (5.2.2) and (5.2.4), $\pi^*_{x_i}$ and $\pi^*_{x_{1i}}$ are strictly positive. Additionally, $\pi^*_{h_{1i}}$ and $\pi^*_{h_{2i}}$ are strictly positive from the equilibrium version of (5.2.3) and (5.2.4) hence so is π^*_{hi}. Then using inequality (5.5.24):

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

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

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

then the proof of Theorem 1.5.1 follows as in the proof of Theorem 3.1.1 of Al-Fwzan (2015).

We conclude that the proof of 5.5.1 is different to Al-Fwzan (2015) particularly at the beginning. We needed to re-express the disease transmission term in terms of β^* and β^*_h for the proof to work. It is a more complicated and significantly different proof because of the needle equations. Also R_0 is the same for the Pessimistic Model with both Assumption 1 and Assumption 2. There is a difference between the results for Assumption 1 and Assumption 2 in that the $\beta^*_{h_{1j}}$ and $\beta^*_{h_{2j}}$ value differs.

However, the prediction of what happens when $0 \leq R_0 \leq 1$ can be answered by the following theorem. The theorem reflects on what happens when R_0 takes the value between 0 and 1 with the notion that HCV in each group of PWIDs and needles in each shooting gallery dies out.

For dealing with the PWID needle interaction assumptions of Corson's model and $\psi = 0$ per year the following theorem corresponds to Theorem 3.1.4 of Al-Fwzan (2015). Our proof is based on the proof of Al-Fwzan (2015) but there are differences because of the PWID-needle interaction assumptions and the treatment of infected PWIDs.

Theorem 5.5.3. *The disease will ultimately die out whatever the initial conditions if* $R_0 < 1$.

Proof. Note that the idea of the proof is similar to that of Al-Fwzan (2015) but the main difference is the needle equations. There is also the treatment rate of infected PWIDs ψ. This outcome is proved in several steps. Recall that the proportion of acutely h_1 infected PWIDs in group i is referred to by $\pi_{h_{1i}}$ and we define $\pi^{\infty}_{h_{1i}} = \limsup_{t\to\infty} \pi_{h_{1i}}(t), i = 1, 2, \ldots, p$. Similarly, we define $\pi^{\infty}_{h_{2i}}$, $\pi^{\infty}_{y_i}$, $\pi^{\infty}_{z_i}$ and $\beta^{\infty}_{h_{1j}}$, $\beta^{\infty}_{h_{2j}}$ and $\beta^{\infty}_{y_j}$ for both assumptions of needles.

We are now going to show that $\pi^{\infty}_{y_i}$, $\pi^{\infty}_{z_i}$, $\beta^{\infty}_{h_{1j}}$, $\beta^{\infty}_{h_{2j}}$ and $\beta^{\infty}_{y_j}$ can all be bounded above with bound involving $\pi^{\infty}_{h_{1k}}$ and $\pi^{\infty}_{h_{2k}}$, $k = 1, 2, \ldots, p$. We shall start off the proof by giving an upper bound in terms of $\pi^{\infty}_{h_{1i}}$ and $\pi^{\infty}_{h_{2i}}$ for the upper limit suprema $\pi^{\infty}_{y_i}$, $\beta^{\infty}_{h_{1j}}$, $\beta^{\infty}_{h_{2j}}$ and $\beta^{\infty}_{y_j}$ in each group of PWIDs i and shooting gallery j. A proof of several results that give upper bounds is paramount given that each group i of PWIDs and shooting gallery j in terms of the limit supremum $\pi^{\infty}_{h_{1i}}$ or $\pi^{\infty}_{h_{2i}}$. From equation (5.2.3) and equation (5.2.4), there is a link between $\pi^{\infty}_{h_{1i}}$ and $\pi^{\infty}_{h_{2i}}$. Therefore, taking into consideration the proof of theorem 2.4.2 in Chapter 2 and applying this result will complete our proof with the following anticipation:

Lemma 5.5.4. $\pi^{\infty}_{y_i} \leq \frac{\sigma\pi^{\infty}_{h_{1i}}}{\mu+\psi}$.

Proof. From equation (5.2.5), we have that

$$\frac{d\pi_{y_i}}{dt} + (\mu + \psi)\pi_{y_i} = \sigma\pi_{h_{1i}}.$$

So given $\epsilon > 0$, there exists $t \geq t_0(\epsilon)$ and

$$\begin{aligned}\frac{d}{dt}[\pi_{y_i}\exp((\mu+\psi)t)] &= \sigma\pi_{h_{1i}}\exp((\mu+\psi)t),\\ &\leq \sigma(\pi^{\infty}_{h_{1i}} + \epsilon)\exp((\mu+\psi)t), \qquad \forall t \geq t_0(\epsilon) \quad \text{and} \quad \epsilon > 0.\end{aligned}$$

Let $t \geq t_0(\epsilon)$ and integrating over $[t_0(\epsilon), t]$ gives

$$\begin{aligned}\pi_{y_i}(t) &\leq \pi_{y_i}(t_0(\epsilon))\exp(-(\mu+\psi)(t-t_0(\epsilon))) \\ &\qquad + (\pi^{\infty}_{h_{1i}}+\epsilon)\sigma\frac{1}{\mu+\psi}(1-\exp[-(\mu+\psi)(t-t_0(\epsilon))]), \\ &\leq \epsilon + (\pi^{\infty}_{h_{1i}}+\epsilon)\sigma\frac{1}{\mu+\psi}, \qquad\qquad \forall t \geq t_1(\epsilon) > t_0(\epsilon).\end{aligned}$$

Letting $t \to \infty$ and choosing $\epsilon_1 = \epsilon\big(\frac{\mu+\psi+\sigma}{\mu+\psi}\big)$, we have that:

$$\pi^{\infty}_{y_i} \leq \frac{\sigma\pi^{\infty}_{h_{1i}}}{\mu+\psi} + \epsilon_1.$$

Therefore the result follows as ϵ_1 is positive and arbitrary. Using the same method which was used in the previous proof of Lemma then we have that:

$$\pi^{\infty}_{z_i} \leq \frac{\sigma\alpha\pi^{\infty}_{h_{2i}}}{\mu}. \tag{5.5.26}$$

Under Assumption 1 for needles, from equation (5.2.7) we have

$$\begin{aligned}\frac{d\beta_{h_{1j}}}{dt} &= \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}} - \beta_{h_{1j}}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij}+\tau_j\bigg) - \beta_{h_{1j}}\sum_{i=1}^{p}\pi_{h_{1i}}\Lambda_{ij}(1-\phi_{lj}) \\ &\leq \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}} - \beta_{h_{1j}}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij}+\tau_j\bigg)\end{aligned}$$

hence, using a similar argument as in Lemma 5.5.4 then we can show that

$$\beta^{\infty}_{h_{1j}} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_{1i}}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}.$$

Now in stage acute h_2, from equation (5.2.8) we have:

$$\begin{aligned}\frac{d\beta_{h_{2j}}}{dt} &= \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}} - \beta_{h_{1j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}}(1-\phi_{ij}) - \beta_{h_{2j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}}(1-\phi_{ij}) \\ &\qquad - \beta_{h_{2j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}}(1-\phi_{ij}) - \beta_{h_{2j}}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij}+\tau_j\bigg), \\ &\leq \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}} - \beta_{h_{2j}}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij}+\tau_j\bigg).\end{aligned}$$

Again by using a similar argument on Lemma (5.5.4) then we have

$$\beta^{\infty}_{h_{2j}} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_{2i}}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}.$$

Under Assumption 2 for needles, from equation (5.2.9) we have

$$\begin{aligned}\frac{d\beta_{h_{1j}}}{dt} &= \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}} - \beta_{h_{1j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}}(1-\phi_{ij}) - \beta_{h_{1j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}}(1-\phi_{ij}) \\ &\quad - \beta_{h_{1j}}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij} + \tau_j\bigg), \\ &\leq \sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}} - \beta_{h_{1j}}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij} + \tau_j\bigg).\end{aligned}$$

Therefore,

$$\beta^{\infty}_{h_{1j}} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_{1i}}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}.$$

Similarly in stage acute h_2, from equation (5.2.10) we have that:

$$\beta^{\infty}_{h_{2j}} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_{2i}}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}.$$

For both Assumptions, from equation (5.2.11) we have that:

$$\begin{aligned}\frac{d\beta_{y_j}}{dt} &= \sum_{i=1}^{p}\Lambda_{ij}\pi_{y_i} - \beta_{h_{1j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{y_i}(1-\phi_{ij}) - \beta_{h_{2j}}\sum_{i=1}^{p}\Lambda_{ij}\pi_{y_i}(1-\phi_{ij}) \\ &\quad - \beta_{y_j}\sum_{i=1}^{p}\Lambda_{ij}\pi_{y_i}(1-\phi_{ij}) - \beta_{y_j}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{1i}}(1-\phi_{ij}) - \beta_{y_j}\sum_{i=1}^{p}\Lambda_{ij}\pi_{h_{2i}}(1-\phi_{ij}) \\ &\quad - \beta_{y_j}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij} + \tau_j\bigg). \\ &\leq \sum_{i=1}^{p}\Lambda_{ij}\pi_{y_i} - \beta_{y_j}\bigg(\sum_{i=1}^{p}\Lambda_{ij}\phi_{ij} + \tau_j\bigg).\end{aligned}$$

Thus,

$$\beta^{\infty}_{y_j} \leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{y_i}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}.$$

Therefore we conclude that for both Assumption 1 and Assumption 2 we have that:

$$\begin{aligned}\beta^{\infty}_{h_{1j}} &\leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_{1i}}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}, \\ \beta^{\infty}_{h_{2j}} &\leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{h_{2i}}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}, \\ \beta^{\infty}_{y_j} &\leq \frac{\sum_{i=1}^{p}\Lambda_{ij}\pi^{\infty}_{y_i}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j},\end{aligned} \tag{5.5.27}$$

so, it is clear that our $\beta^{\infty}_{h_{1j}}$, $\beta^{\infty}_{h_{2j}}$ and $\beta^{\infty}_{h_{yj}}$ are bounded differently than Al-Fwzan (2015) because of the factor $(\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j)$ in the denominator. □

Define $\pi_{h_k} = \pi_{h_{1k}} + \pi_{h_{2k}}$. π_{h_k} refers to the proportion of PWIDs in group k who are infected and in the acute stage

Lemma 5.5.5. *For each $i = 1, 2, \ldots, p$:*

$$\pi^{\infty}_{hi} = \frac{\pi^{\infty}_{h_{1i}}}{(1-\delta)} = \frac{\pi^{\infty}_{h_{2i}}}{\delta}.$$

Proof. Following a similar proof of Lemma 3.1.6 in Al-Fwzan (2015). □

Lemma 5.5.5 can be used in writing the inequality in Lemma 5.5.4 and inequalities (5.5.26) and (5.5.27) in terms of $\pi^{\infty}_{h_i}$ to obtain:

$$\pi^{\infty}_{y_i} \leq \frac{\sigma(1-\delta)\pi^{\infty}_{h_i}}{\mu + \psi}, \tag{5.5.28}$$

$$\pi^{\infty}_{z_i} \leq \frac{\sigma\delta\alpha\pi^{\infty}_{h_i}}{\mu}, \tag{5.5.29}$$

$$\beta^{\infty}_{h_{1j}} \leq \frac{\sum_{i=1}^{p} \Lambda_{ij}(1-\delta)\pi^{\infty}_{h_i}}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j}, \tag{5.5.30}$$

$$\beta^{\infty}_{h_{2j}} \leq \frac{\sum_{i=1}^{p} \Lambda_{ij}\delta\pi^{\infty}_{h_i}}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j} \quad \text{and} \tag{5.5.31}$$

$$\beta^{\infty}_{y_j} \leq \frac{\sigma(1-\delta)}{(\mu+\psi)} \frac{\sum_{i=1}^{p} \Lambda_{ij}\pi^{\infty}_{h_i}}{\sum_{l=1}^{p} \Lambda_{lj}\phi_{lj} + \tau_j}. \tag{5.5.32}$$

Now, we have

$$\frac{d}{dt}\pi_{h_i} = \sum_{j=1}^{q} (1 - \pi_{h_i} - \pi_{y_i} - \pi_{z_i})\lambda_i P_{ij}(1-\phi_{ij})(\alpha_h(\beta_{h_{1j}} + \beta_{h_{2j}}) + \alpha_y\beta_{y_j}) - (\mu+\sigma)\pi_{h_i}.$$

Hence given $\epsilon > 0$, there exists $t_4 \geq t_0$ such that for $t_4 \leq t$:

$$\begin{aligned}
\frac{d}{dt}\pi_{h_i} &\leq (1-\pi_{h_i})\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})(\alpha_h(\beta^{\infty}_{h_{1j}}+\beta^{\infty}_{h_{2j}})+\alpha_y\beta^{\infty}_{y_j}+\epsilon)-(\mu+\sigma)\pi_{h_i},\\
&\leq (1-\pi_{h_i})\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\\
&\qquad\left[\frac{\alpha_h(\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{h_{1k}}+\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{h_{2k}})+\alpha_y\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{y_k}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}+\epsilon\right]-(\mu+\sigma)\pi_{h_i},\\
&\leq (1-\pi_{h_i})\left[\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})\left(\alpha_h+\alpha_y\frac{\sigma}{(\mu+\psi)}(1-\delta)\right)\right.\\
&\qquad\left.\left(\frac{\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{h_k}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}+\epsilon_1\right)\right]-(\mu+\sigma)\pi_{h_i},\\
&= (\mu+\sigma)\left[(1-\pi_{h_i})\left(\sum_{j=1}^{q}\frac{\lambda_i P_{ij}(1-\phi_{ij})\xi\sum_{k=1}^{p}\Lambda_{kj}\pi^{\infty}_{h_k}}{\sum_{l=1}^{p}\Lambda_{lj}\phi_{lj}+\tau_j}+\epsilon_{2i}\right)-\pi_{h_i}\right],\\
&= (\mu+\sigma)\left[(1-\pi_{h_i})\left(\sum_{k=1}^{p}Q^*_{ik}\pi^{\infty}_{h_k}+\epsilon_{2i}\right)-\pi_{h_i}\right],
\end{aligned}$$

where $\epsilon_1 = \epsilon/(\xi(\mu+\sigma))$, $\epsilon_{2i} = \epsilon_1\xi\sum_{j=1}^{q}\lambda_i P_{ij}(1-\phi_{ij})$, and $\boldsymbol{Q}^*$ is a matrix defined earlier. Recall that R_0 is the spectral radius of $\boldsymbol{Q}^*$ and $R_0 = \rho(\boldsymbol{Q}^*) \leq 1$. Therefore we have:

$$\frac{d}{dt}\pi_{h_i} \leq (\mu+\sigma)\left[\left(\sum_{k=1}^{p}Q^*_{ik}\pi^{\infty}_{h_k}+\epsilon_{2i}\right)-\pi_{h_i}\left(1+\sum_{k=1}^{p}Q^*_{ik}\pi^{\infty}_{h_k}+\epsilon_{2i}\right)\right].$$

Hence,

$$\pi^{\infty}_{h_i} \leq \frac{\sum_{k=1}^{p}Q^*_{ik}\pi^{\infty}_{h_k}+\epsilon_{2i}}{1+\sum_{k=1}^{p}Q^*_{ik}\pi^{\infty}_{h_k}+\epsilon_{2i}}.$$

As ϵ is arbitrary then letting $\epsilon \to 0$ and $\epsilon_{2i} \to 0$ we conclude that:

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

Now if we assume that for some i_0 $\pi^{\infty}_{h_{i_0}} > 0$ and following similar way as Al-Fwzan (2015), then we have that there exists $\epsilon_2 > 0$ such that:

$$\pi^{\infty}_{h_i}(1+\epsilon_2) \leq \sum_{k=1}^{p}Q^*_{ik}\pi^{\infty}_{h_k},$$

so we have

$$\boldsymbol{\pi}^{\infty}_{h}(1+\epsilon_2) \leq \boldsymbol{Q}^*\boldsymbol{\pi}^{\infty}_{h},$$

hence

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

As this contradicts the fact that R_0 is less than one every $\pi_{h_k}^{\infty} = 0$. As in Al-Fwzan (2015) considering all of the infectious PWID classes and the previously infected susceptible class the limsups are all zero. Note that the details to show this are not exactly the same because of the different needle equations and the treatment of infected PWIDs being included but the underlying principle is the same. Hence, the proof of the global stability of the disease-free equilibrium solution is complete when $R_0 \leq 1$.

5.6 Parameters and numerical simulations

We are following the structure of the chapter four in Al-Fwzan's thesis because we want to compare the results between the two models. The primary course of conducting the simulation results is to estimate the impacts of the HCV during the time interval of 70 years. The estimated production of HCV prevalence simulation results over time is through the model parameters. In this section, the assumption that the model portrays similar characteristics in shooting galleries is kept into consideration. This implies that the PWID group share in one shooting gallery ($q = 1$). To be simple, we use this assumption and discuss the heterogeneous cases of shooting galleries. The simulation results under the assumption of homogeneity of shooting galleries are performed to illustrate the prevalence of HCV among different groups of PWIDs. In addition to our assumption of homogeneity of shooting galleries, we also have an assumption that all the model parameters are homogeneous, except for the needle sharing rates.

5.6.1 Al-Fwzan's model and our model

As we have mentioned in the differences between our model and Corson's model it is also the same here, our model is based on the 'pessimistic assumption' of Lewis and Greenhalgh (2001) and Al-Fwzan's model is based on the 'optimistic assumption' of Corson (2011). Moreover we have also introduced the rate of treatment ψ in

our model which was not considered in Al-Fwzan's model. Hence there are two differences between our model and Al-Fwzan's model:

1. The PWID - needle interactions have been varied.

2. A treatment term has been considered.

Therefore there are two opposing factors in our model. Because the PWID needle interaction terms are more pessimistic we expect the disease to spread faster. However because of the disease treatment term the disease will spread slower. Hence overall we are not able to say whether or not the disease will spread faster or slower in our model compared with Al-Fwzan's model.

5.6.2 Parameters used

This section contains the presentation of the numeric estimations of the parameters of the model. The use of many of these parameter estimations is evident in Chapter Three and they have also been used together with other parameters in the study of the effects of heterogeneity of the HCV prevalence among a variety of PWID groups. We then proceed to discuss the estimation of the parameters.

Heterogeneity in the rates of sharing is the only heterogeneity of our model in our simulation in this chapter. We will thus put the parameter under discussion in a more detailed manner and give an insight into the different rates for each different group in our simulation. Contrary to what has been observed in the PWID population, many studies assumed homogeneous sharing rates for simplicity (Kaplan and O'Keefe (1993), Corson (2011) and Corson et al. (2012)). A mean of 72.48 per year of shared injection rate for Glasgow PWIDs was assumed by Goldberg et al. (1995) in studies of HIV transmission amongst PWIDs. 103 per year was the mean found by Corson et al. (2012) after obtaining λ from survey data of PWIDs from Glasgow during 1990-1993 and 2007.

Our focus is mainly on the heterogeneity of the rate of sharing needles among PWIDs in different groups i, for $i = 1, 3, 5$ and 9. In this simulation we aim at discussing how the prevalence of HCV in a population of PWIDs and shooting galleries is affected by heterogeneity. As in Al-Fwzan (2015), the probability of

sharing borrowed needles that were previously used by another PWID is presented by the data of a survey of PWIDs in Glasgow collected by HPS (Hutchinson et al. (2000)). These sharing rates of borrowed used needles, which were obtained by HPS during 1990-1993 detailing sharing over the past six months. We simulated data of sharing rates among people who were PWIDs in Glasgow collected by Goldberg et al. during six months amongst a sample of 503 PWIDs in 1990 to attempt to compare a variety of sets of data in sharing needle rates (Goldberg et al. (1995)). We first had an assumption that the model is homogeneous. We then proceeded to separate the PWIDs population into three groups in accordance with their sharing rates. Following that we separated the PWIDs into five groups and nine groups with different sharing rates. We follow simulations performed in Al-Fwzan (2015) so that we can compare the results with Al-Fwzan (2015).

5.6.3 Simulation results

We are following the structure of Al-Fwzan's thesis so that we can obtain new results with the pessimistic PWID-needle interaction assumptions and examining the effect of treatment on those results. Therefore, data from Glasgow assisted us to start our simulation with different sharing rates of different groups. 9,000 PWIDs that mix heterogeneously is what makes the population size. The behavior of the disease in each different group is explored after we have divided the population into groups. $\lambda = 167.39$ per year is what we found to be the sharing rate of λ in the whole population of PWIDs in the first group. The values of different sharing rates in each different group and the number of PWIDs are illustrated in Table 5.3. The aim of presenting the results of the model simulation is to demonstrate the effect of heterogeneity of the prevalence of HCV among p groups of PWIDs. We used the above parameter values for the model for $p = 1, 3, 5$ and 9 and $q = 1$ shooting gallery to calculate the model graph. As mentioned earlier, the group sizes and sharing rates for each group were taken from a survey of PWIDs in 1990. Information from Corson et al. (2012) provided the estimates of the rest of the model parameters. The set of parameter estimations and their definitions are shown in Table 5.2. We have the assumption that every PWID in group i will choose a needle in shooting gallery j

since $j = 1$. To simplify, we considered $P_{ij} = 1$ in this stage of discussion. We estimated the number of needles to be $m = 8,932.03$ and the number of PWIDs at $n = 9,000$. The information from the model of Corson et al. (2012), who take $\gamma = 1.002$ as the ratio of PWIDs to needles, is what was used to provide the figure for the number of needles (Griesbach et al. (2006) and King et al. (2009)). We then estimated that Λ_{ij}, the arrival rate of a single PWID in group i at a needle in shooting gallery j:

$$\Lambda_{ij} = \frac{\lambda_i n_i}{m_j} \qquad i = 1, 3, 5 \quad \text{and} \quad 9, \quad j = 1.$$

Estimation of the basic reproduction number (R_0)

Some of the parameters on which these numbers depend being difficult, if not impossible, to quantify directly estimate reproduction numbers to be typically a complicated process. This parameter determines a threshold: whenever $R_0 > 1$, a typical infective gives rise, on average, to more than one secondary infection, leading to an epidemic. To explore disease behavior, we need to estimate this threshold we estimate R_0 using Table 5.3 and Table 5.2 and our expression of this number, which is:

$$R_0 = \xi \frac{\sum_{k=1}^{p} \lambda_k^2 n_k (1-\phi)}{m\big(\sum_{l=1}^{p} \frac{\lambda_l n_l \phi}{m} + \tau\big)}, \tag{5.6.33}$$

where $\xi = (\alpha_y \sigma(1-\delta) + \alpha_h(\mu+\psi))/(\mu+\psi)(\mu+\sigma)$. This corresponds to equation (4.1) of Al-Fwzan (2015) except that the definition of ξ and the denominator of the fraction have been modified. In each stage of our simulation, we estimate R_0 using the sharing rates in the different groups.

5.6.4 Comparison of models with different numbers of groups of infectious PWIDs

For all the four models, we aim to incorporate the total proportions of infected PWIDs. Figure 5.1 shows the plots of these proportions of infected PWIDs in Glasgow using data from 1990 (Hutchinson et al., 2000). The highest equilibrium

proportion of infectious PWIDs occurs in a single group model (homogeneous), while the ninth group (heterogeneity model) has the lowest overall equilibrium prevalence. This is an indication that for this observed data, the reduction of the overall endemic equilibrium level of disease among PWIDs may be caused by increasing the heterogeneity of the PWIDs. The observed distribution of needle sharing rate being very skew is the reason for this. The prevalence in the smaller groups gets higher with the increase in heterogeneity while that of higher larger groups gets lower, overall the endemic prevalence decreases.

It is moreover shown in Figure 5.1 that the behavior of infectious PWIDs in the five and nine group models is similar, the total production of infectious PWIDs in Table 5.5 can also attest to this. The increase of the initial speed of increase of the epidemic (which is related to R_0) is subsequent to the increase in the number of groups. So our theoretical results which show that in this situation, the homogeneous model has the lowest value of R_0 are consistent with our simulations. The basic reproductive number is shown for each model, and we can see that the five and nine group models have the highest number for R_0, as presented in Table 5.3.

Furthermore, the endemic equilibrium prevalence values in each stage: susceptible, acute, chronic, and immune, and the number of groups is compared in Table 5.1. We can, therefore, see that the decrease in the endemic equilibrium prevalence of infectious PWIDs is subsequent to an increase in the number of groups. This indicates that a reduction in the long term endemic equilibrium proportion of HCV among this population may be as a result of increasing the heterogeneity in the PWIDs population.

The R_0, and equilibrium solutions for both PWIDs and needles are evaluated and calculated in each model. For every seventy years, we calculate the overall proportions of infectious PWIDs and needles against time. The results for all the four models are summarized in 5.4. You should note that the value of R_0 calculated is much higher than those generally observed for homogeneous models as in Al-Fwzan (2015). The simulations results presented in Table 5.4 indicate that as the number of groups increases R_0 values increase and the overall prevalence of HCV amongst PWIDs and needles decreases. Also the values of R_0 are higher than the

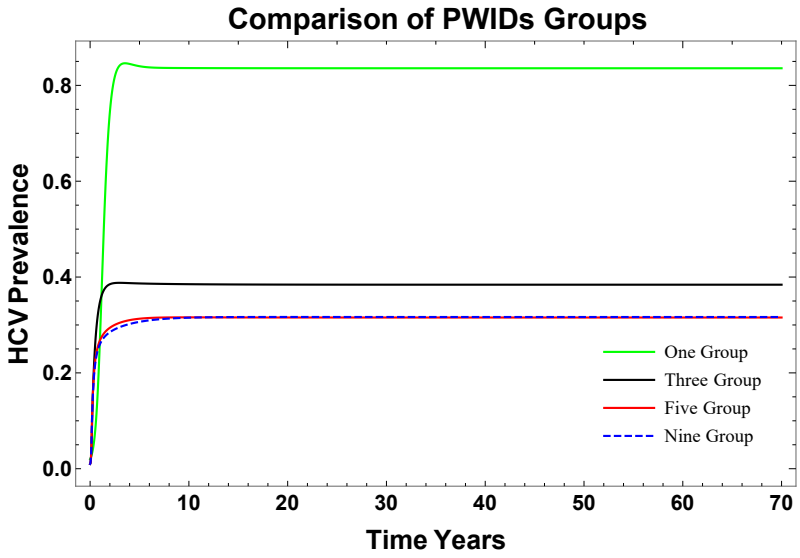

Figure 5.1: The proportions of PWIDs in Glasgow in the four models using data from 1990.

corresponding values in the model discussed in Table 4.4 of Al-Fwzan (2015) and the greater the amount of heterogeneity, i.e. the greater the number of groups, the bigger the difference gets.

Table 5.1: Comparing the endemic equilibrium proportions of infectious PWIDs for all four models using data from 1990.

Models	π_x^*	$\pi_{x_1}^*$	$\pi_{h_1}^*$	$\pi_{h_2}^*$	π_y^*	π_z^*
One group	0.1232	0.0231	0.1232	0.0212	0.7098	0.0624
Three group	0.6296	0.0111	0.0367	0.0129	0.2718	0.0379
Five group	0.6845	0.0154	0.0306	0.0108	0.2270	0.0317
Nine group	0.7009	0.0147	0.0290	0.0102	0.2151	0.0300

5.6.5 The effect of treatment on the basic reproduction number with different numbers of groups

In this subsection, we will see that the changed basic reproduction number values which result from different ψ parameters. We run simulations utilizing three unique

Table 5.2: Table of parameter estimates used in our simulations (Adapted from Al-Fwzan (2015)).

Parameter	**Definition**	**Estimate**
ϕ_{ij}	Probability that a PWID in group i successful needle cleaning in shooting gallery j before use, $i = 1, 3, 5$ and 9, $j = 1$.	0.255
λ_i	Needle and syringe sharing rate in group i, $i = 1, 3, 5$ and 9.	Table 5.3
τ_j	Needle turnover rate in shooting gallery j, $j = 1$.	133 per year
μ	Rate PWIDs leave the sharing, injecting population.	0.17 per year
α_h	Acute HCV transmission probability.	0.0432
α_y	Chronic HCV transmission probability.	0.016
$1/\sigma$	Duration of the acute HCV phase.	0.5 years
δ	Proportion of infected PWIDs that resolve HCV infection.	0.26
α	Proportion of PWIDs that become immune.	0.25
P_{ij}	The probability that a PWID in group i chooses shooting gallery j to share a needle.	1
m_j	Number of needles in shooting gallery j, $j = 1$.	8,982
ψ	Per capita treatment rate.	0.1 per year

estimations of ψ relating to our present parameter value $\psi = 0.1$ per year, $\psi = 0.03$ per year which was estimated by Martin et al. (2015) and $\psi = 0.06$ per year which was estimated by Martin et al. (2011).

Table 5.5 shows the increasing on the rate of treatments leads to decrease in the basic reproduction numbers in all groups model. Also we can see that the largest decrease in the value of the basic reproduction number occurs in the nine group

One Group Model

λ 167

n 9000

Three Group Model

λ_1 0.000 λ_2 152.44 λ_3 1440.25

n_1 5135.08 n_2 3157.25 n_3 707.66

Five Group Model

λ_1 0.000 λ_2 34.91 λ_3 364.75 λ_4 550.9 λ_5 1996.09

n_1 5135.08 n_2 2032.25 n_3 1125 n_4 272.18 n_5 435.48

Nine Group Model

λ_1 0.000 λ_2 19.55 λ_3 91.25 λ_4 231.43 λ_5 423.66 λ_6 462.67 λ_7 651.78 λ_8 1629.46 λ_9 2607.14

n_1 5135.08 n_2 1596.77 n_3 435.48 n_4 344.75 n_5 780.24 n_6 145.16 n_7 127.01 n_8 272.17 n_9 163.3

Table 5.3: Shared needles and syringes rate λ_i, sizes of group n_i of PWIDs for $i = 1, 3, 5, 9$ using data from 1990. (Adapted from Al-Fwzan (2015)).

Table 5.4: Comparing the four models in the basic reproductive number and equilibrium percentage of proportion of infectious PWIDs and infectious needles using data from 1990.

Model	R_0	**Infectious PWIDs**	**Infectious needles**
One group	7.15	84%	45%
Three group	43.92	37%	49%
Five group	56.13	32%	50%
Nine group	59.28	31%	51%

model and the smallest decrease value in the one group model.

Therefore, we expect that when we decrease the rate of treatment then the disease will spread faster in our model and vice-versa. Note also this effect is more pronounced, at least in absolute values, the greater the amount of heterogeneity in the model.

Table 5.5: Comparing the four models in the basic reproduction number values with $\psi = 0.03$ per year, $\psi = 0.06$ per year and $\psi = 0.1$ per year.

Model	$\psi = 0.03$ per year	$\psi = 0.06$ per year	$\psi = 0.1$ per year
One group	8.82	7.98	7.15
Three group	54.21	49.03	43.92
Five group	70.82	64.05	56.13
Nine group	73.17	66.18	59.28

Table 5.6: Comparing the one group model in the basic reproductive number and equilibrium percentage of proportion of infectious PWIDs and infectious needles between our model and Al-Fwzan's (2015) model using data from 1990.

One group model	R_0	**Infectious PWIDs**	**Infectious needles**
Al-Fwzan's results	5.8	79%	42%
Our results with $\psi = 0.1$ per year	7.1	84%	45%
Our results with $\psi = 0.0$ per year	9.9	87%	48%

Table 5.7: Comparing the three group model in the basic reproductive number and equilibrium percentage of proportion of infectious PWIDs and infectious needles between our model and Al-Fwzan's (2015) model using data from 1990.

Three group model	R_0	**Infectious PWIDs**	**Infectious needles**
Al-Fwzan's results	35	28%	48%
Our results with $\psi = 0.1$ per year	43.9	37%	49%
Our results with $\psi = 0.0$ per year	61.2	39%	51%

Table 5.8: Comparing the five group model in the basic reproductive number and equilibrium percentage of proportion of infectious PWIDs and infectious needles between our model and Al-Fwzan's (2015) model using data from 1990.

Five group model	R_0	**Infectious PWIDs**	**Infectious needles**
Al-Fwzan's results	45.7	23%	45%
Our results with $\psi = 0.1$ per year	56.1	32%	50%
Our results with $\psi = 0.0$ per year	78.2	34%	52%

Table 5.9: Comparing the nine group model in the basic reproductive number and equilibrium percentage of proportion of infectious PWIDs and infectious needles between our model and Al-Fwzan's (2015) model using data from 1990.

Nine group model	R_0	**Infectious PWIDs**	**Infectious needles**
Al-Fwzan's results	48.3	27%	44%
Our results with $\psi = 0.1$ per year	59.3	31%	51%
Our results with $\psi = 0.0$ per year	82.6	32%	52%

5.6.6 Comparison between our results with $\psi = 0.0$ per year and $\psi = 0.1$ per year with different numbers of groups and the results of Al-Fwzan (2015)

Because our model is based on the 'pessimistic assumption' of Lewis and Greenhalgh (2001) and Al-Fwzan's model is based on the 'optimistic' assumption of Corson (2011) therefore we expect that if $\psi = 0.0$ per year then both R_0 and the proportions of infectious PWIDs and needles would be higher in our model than $\psi = 0.1$ per year. With $\psi = 0.1$ per year these values are lower but still higher than Al-Fwzan's model because the effect of changing the PWID-needle assumptions is higher than

R_0	One group	Three group	Five group	Nine group
Our R_0 results with $\psi = 0$ per year	9.9	61.2	78.2	82.6
Our R_0 results with $\psi = 0.1$ per year	7.1	43.9	56.1	59.3
Al-Fwzan's (2015) results	5.8	35	45.7	48.3

Table 5.10: Comparison between our R_0 results with $\psi = 0$ per year and $\psi = 0.1$ per year in different numbers of groups and Al-Fwzan's (2015) results.

the effect of introducing treatment. For the one group model these results are clear from Table 5.6.

As for the one group model, when we compare our results with the results of Al-Fwzan (2015) then it is clear that our R_0 value is bigger in our model than the value of R_0 obtained for Al-Fwzan's model. Moreover, long-term prevalence of HCV in our model is bigger than long-term prevalence of HCV obtained for Al-Fwzan's model (see Table 5.7).

Also, if we are comparing between our simulation results and Al-Fwzan's (2015) results for five group model therefore a similar scenario happens in Tables 5.8 as for the one group model and the three group model.

Lastly, as one group model, three group model and five group model therefore it is clear that when we compare our results with Al-Fwzan's (2015) results then our R_0 value and long-term prevalence of HCV are bigger in our model than the values of R_0 and long-term prevalence of HCV obtained for Al-Fwzan's model (see Table 5.9).

5.6.7 Comparison between our R_0 results with different numbers of groups and the results of Al-Fwzan (2015)

As we have shown in a previous chapter, our model is similar to the 'Pessimistic Model' of HIV transmission amongst PWIDs studied by Lewis and Greenhalgh (2001a) and Al-Fwzan's model is similar to the 'Optimistic Model' studied by Cor-

son (2011) and Corson et al. (2012). Therefore we predict that disease will spread faster in our model so our R_0's value will be larger than the corresponding R_0 in the results of Al-Fwzan (2015) if $\psi = 0.0$ per year.

Note that values of R_0 in our model will be larger than the the results of Al-Fwzan (2015) (see Tables 5.6, 5.7, 5.8, 5.9 and 5.10) even though we have considered treatment of infected PWIDs into the model. This is because we have changed the PWID needle interaction assumptions from the optimistic PWID needle interaction assumptions of Al-Fwzan (2015) to the pessimistic PWID needle interaction assumptions of Lewis and Greenhalgh (2001a). Changing the PWID needle interaction assumptions increases R_0 and this more than offsets the reduction due to introducing treatment of PWIDs.

5.7 Conclusion

In this chapter we have formulated a mathematical model of the effect of heterogeneity on the prevalence of HCV, building on the models developed by Corson et al. (2012), Al-Fwzan (2015) and Greenhalgh (1996). A system of differential equations has been derived to describe the progress of the disease. Moreover our model is different than the model discussed in Al-Fwzan (2015) because of the PWID needle interactions and the ψ term.

We have investigated analytically the results and behaviour of our basic HCV transmission model. A key parameter of our model is the basic reproductive number R_0. Analysis indicates that the model is governed by the basic reproductive number R_0. It has been shown that if $R_0 \leq 1$ and the disease is present at the start in the population, then the system will tend towards the globally stable DFE. We believe that it is possible to go further i.e. to modify the proof of Theorem 3.1.7, Theorem 3.1.8, Theorem 3.1.15 and Theorem 3.1.16 in Al-Fwzan's thesis for our model, also if $R_0 > 1$ there is an endemic equilibrium solution but we have not pursued this because of lack of space.

Moreover, we have developed numerical simulation on the system of equations (5.2.1)-(5.2.11) describing the spread of hepatitis C amongst PWIDs. We started

with a literature review to identify values for the relevant parameters. Then we performed some simulation results using data from a survey of PWIDs in 1990.

After that we have assumed that there is one shooting gallery where all PWIDs share needles. Then we divide the PWID population into different numbers of groups with different sharing rates. As the number of groups increased also R_0 increased. The initial rate of increase of the level of disease also increased with the number of groups as did the endemic equilibrium prevalence of HCV amongst needles. Also we have compared our R_0 results with different numbers of groups and those of Al-Fwzan (2015) results when we have introduced treatment and without treatment.

Chapter 6

Conclusions and Future Work

We started off the thesis with a literature survey and we have added a new section on the epidemic models and new subsection on the local and global asymptotic stability of the ODEs. Also, we have discussed in new sections the bifurcation and persistence and Quasi-steady-state approximation. After that we have introduced in general that the technical way to calculate R_0 then we have presented the special case how we calculate R_0 in our model. Therefore, we have discussed the next generation matrix method to derive the basic reproduction number. Lastly, we discuss some heterogeneity models such as the model of Greenhalgh (1996) and the model of Al- Fwzan and Greenhalgh (2015).

Moreover we have developed a model to approximate HCV transmission among Glasgow PWIDs, building on the models developed by Corson (2011) and Corson et al. (2012). Our model is different than the model discussed in Corson's works because of the PWID needle interactions and the ψ term. Also we have calculated our R_0 by using the next generation matrix method for both the full and approximate models and also given an alternative derivation to Corson's model. A major novel innovation in our model compared to Corson (2011), Corson et al. (2012) and the other previous models is that we introduce a different set of needle equations. In Corson (2011) and Corson et al. (2012) when an infected individual PWID uses a syringe or needle after use the syringe or needle takes on the infectious state of that PWID. So once a syringe is infected it remains infected indefinitely. Based on this

we assume that needles and syringes can only move up the levels of infectiousness. Also a second important novel aspect of our model compared to these models is that we have also introduced the effect of treatment of chronically infected PWIDs.

Also we formulated some forms of preventive measures to reduce HCV prevalence in the general public. To achieve this goal, it was, therefore, crucial to understand how injection prone PWIDs interact among their respective groups. To this end, the selected PWID population splits into two risk groups based on the differences in the degree of risk behaviours (Sutton et al. (2006), Roy et al. (2007), Mehta et al. (2011), Corson (2011) and Corson et al. (2013)). As the research progresses, the PWID population is further diversified based on infection status. This form of diversification creates two distinct groups. The difference between these two groups is the level of experience that each group of users has. The experience discussed is on the factor of injecting career or duration, which classified the participants into naive and experienced injecting PWIDs.

Lastly we showed the formulation of a mathematical model framed on the effect of heterogeneity on HCV prevalence. This model builds on previous versions of the models created by Greenhalgh (1996), Corson (2011), Corson et al. (2012) and Al-Fwzan (2015). Moreover our model differs from that of Al-Fwzan (2015) in that we introduce treatment of infected PWIDs at rate ψ and assume that needles cannot lose infectiousness over time. To better explain this phenomenon, we further came up with differential equations to describe the progress of the disease.

In summary, we have shown both analytically and numerically (through a numerical simulation by using package Wolfram Mathematica version 11.1) that the behaviour of the models are governed by the basic reproduction number R_0, with $R_0 = 1$ a critical threshold for endemic HCV prevalence. Also 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 PWIDs and needles. Furthermore, we have found that provided that $R_0 > 1$ and HCV is initially present in the population, our models will tend towards the endemic equilibrium, provided that certain conditions are satisfied.

Hence this study give us an overview of infectious disease modelling which re-

lates to how mathematical models can be applied to study and control the spread of disease. Thus, as we know that the world is currently fighting the COVID-19 pandemic, which continues to affect people globally. Therefore, it can be given us more motivation to work on creating of SIR or SIS model to predict how to control the spread of COVID-19 through a community (Cooper et al. (2020)). The spread of COVID-19 can be reduced significantly if countries take drastic and necessary interventions when the number of affected individuals is still low. China, for instance, was able to control and reduce COVID-19 infections because the country took immediate extreme measures such as closures and confinement, leading to a decrease in the number of affected people. The study by Cooper et al. (2020) shows that mathematical models can help in the fight against pandemic such as COVID-19.

While on the topic of mathematical models on HCV dynamics and heterogeneity of injecting practices, several interests arise. One of the arising interests revolves around the parameters of social life and their influence on PWIDs. It is, therefore, necessary to investigate characteristic parameters among PWIDs like age and how it affects the HCV dynamics in play today, Kondili et al. (2022) discusses an age-structured computational model for HCV and Ayoub et al. (2018) discusses an age-structured model for hepatitis C in Pakistan and it may be possible to explore a similar model.

Moreover the age parameters should encompass those less than thirty years and those older than thirty. This issue of age would also assist researchers in determining the reproduction number of the disease and the conditions that influence the transmission process along with both age groups (Anderson and May (1992)).

One more interesting point of review would be investigating the use of injecting paraphernalia. This research should be on the heterogeneity of how sharing the injecting apparatus pushes the spread of HCV among injecting drug users. Another area of interest should be on a combination of HCV treatment and needle and syringe sharing heterogeneity. This aspect of research should focus on how needle sharing rates modify HCV prevalence among PWIDs. It would also be of significant interest to extend the model to go beyond its current scope of drug users. This move would incorporate two new main groups of drug users. These groups would

comprise of treated PWIDs and another group of untreated PWIDs. This change in dimensions would aim at investigating the dynamics of HCV prevalence between the two groups of participants.

Currently, it is recommending that HCV treatment should as well be offered to individuals who have a high risk of transmitting the disease to other people, including the PWIDs. Based on the recent economic model, it is cost-effective to treat a patient with a moderate stage of fibrosis instead of treating them at the mild stages. Pitcher et al. (2019) review the epidemic modeling literature on HCV transmission and prevention amongst PWIDs and considering treatment. Therefore, there is scope to expand the changing on model's behaviour when we change the rate of treatment.

It is also vital to determine how the emergence of antiviral resistant HCV infections affect the prevalence of HCV amongst PWIDs. To date, there has been no modeling work carried out on the transmission of antiviral resistant HCV infection among PWIDs. Also, it would be interesting to extend the model to prove for the heterogeneous model the existence of a non-zero endemic equilibrium if R_0 exceeds one. The techniques used to prove this are the same ones as discussed in Al-Fwzan (2015).

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