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A mathematical analysis of the financial and medical impact of hepatitis C among drug users in Perth, Western Australia

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A MATHEMATICAL ANALYSIS OF THE FINANCIAL AND MEDICAL IMPACT OF HEPATITIS C AMONG DRUG USERS IN PERTH, WESTERN AUSTRALIA.

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ABSTRACT

The ability of public health planners continues to be hampered by uncertainties encountered with transmissible diseases. Key epidemiological factors such as, how many Western Australian injecting drug users are hepatitis C seropositive or will become infected, duration of intravenous drug use, the intensity of infection, the fraction of those infected that will develop end-stage disease and after how long a period, all combine to limit the ability of a mathematical model to predict future trends.

These models can, however, provide information about certain epidemiological parameters and identify data required to predict future trends. They can be applied to make predictions about the course of infection in the individual and provide a guide to the interpretation of the observed data. This research aims to develop a model of the transmission and spread of hepatitis C, adapting existing models used to predict the spread of HIV and AIDS in one and two sex communities. This model will be used to demonstrate the dynamics and incidence of hepatitis C infection among injecting drug users in Perth, Western Australia.

Predictions derived from the model will then be used to undertake an analysis of the cost of treating those with hepatitis C and cirrhosis related complications, resulting in a prediction of the financial impact of hepatitis C on the Western Australian community.

DECLARATION

I certify that this thesis does not incorporate without acknowledgement and material previously submitted for a degree or diploma in any institution of higher education; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signature:

Date: 09/06/2004

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BACKGROUND TO HEPATITIS C

1.1 Pathophysiology.

The liver is an essential component in the maintenance of life. Not only does it rank first in actual mass, but first in the variety, range and complexity of its functions. It is involved in almost every metabolic function of the body, but is individually responsible for more than 500 separate functions (Price & Wilson, 1982).

Major functions essential for sustaining life include; the formation and excretion of bile, carbohydrate metabolism, protein metabolism, fat metabolism, vitamin and mineral storage, detoxification, and a flood and filter mechanism. Total destruction or removal of the liver results in death within ten hours.

Not only is the liver remarkable for the range of essential functions that it performs, it also possesses a phenomenal regenerative capability. Under normal circumstances only 10-20% of liver tissue needs to be functioning optimally to sustain life. Regeneration of liver tissue remains possible, following assault or disease, when up to 50% of hepatic cells have been damaged or destroyed (Price & Wilson, 1982).

1.1.1 hepatitis C.

In broad terms, hepatitis describes the inflammation of the cells of the liver, where the causative agents include drugs, toxic materials, malignant diseases, alcohol, and micro-organisms, including Epstein-Barr virus, Cytomegalovirus and hepatitis viruses (eg hepatitis A, hepatitis B) (Griffiths-Jones, A 1994).

The hepatitis C virus (HCV) was isolated in 1988 (Choo et.al 1990). Previous to this, all cases of hepatitis not found to be caused by any of the above agents, were listed as hepatitis non-A, non-B. Since its isolation, two other causative viruses in the non-A, non-B hepatitis category have been identified, hepatitis D and hepatitis E. Of the three subgroups, hepatitis C is responsible for the majority of blood-borne non-A, non-B hepatitis cases (Lisanti, P. & Talotta, D. 1994).

Hepatitis C is a single-stranded RNA virus that can be further subdivided into distinct isolates or genotypes. A universal classification system for these genotypes established six major phylum, types1 to 6 where each have several closely related subgroups (ie a to c) (M^{c}Omish, F. et al. 1994). Investigations into a group of false-negative pathology tests among Asian sufferers has lead to the identification of further genotypes, 7, 8 and 9 in Thailand, and types 10 and 11 among Indonesians.

1.1.2 Clinical presentation.

As with all hepatitis viruses, clinical presentation may at best be vague. As many as 50% of people with hepatitis C may be completely asymptomatic (Steven, I.D. et al 1994), and those that do present with symptoms will usually report feelings of tiredness, anorexia, muscle pain, and occasionally right abdominal pain (Griffiths-Jones, A 1994).

While presenting symptoms are either mild or undetectable, at least half the adults with the disease progress to chronic, persistent infection (Hantz, O. et al 1993). In many cases, chronic hepatitis C causes slow, insidious damage to liver cells that often leads

to cirrhosis and hepatocellular carcinoma decades after the initial infection (Hantz, O. et al 1993).

Liver damage, cause by invasion and replication of the virus, consists of inflammation and mononuclear cell infiltration. This occurs in the portal ducts and the parenchyma leading to hepatic cell necrosis. There is a corresponding increase in the size and number of Kupffer cells responsible for the phagocytosis of bacteria and other foreign particles in the blood. Cellular collapse and necrosis is the end result. The accumulation of necrotic tissue in the lobules and ducts of the liver lead to changes in its structure. This change in structure affects all liver functions (Lisanti, P. & Talotta, D. 1994). The progression of these changes to liver functions can be seen on the diagram below, modified from Phipps, Long and Woods (1979).

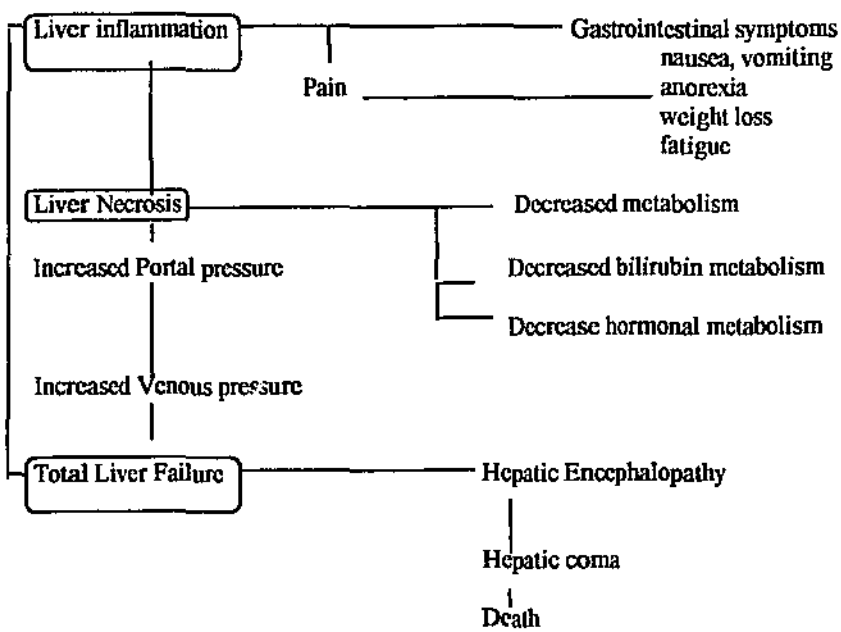

Figure 1. Progression of liver cell failure. Pathophysiology of symptoms that occur in liver disease.

1.1.3 Diagnosis.

Diagnosis is possible through the detection of antibodies by enzyme immunoassay. There is, however a window period of 14 – 180 days (Lisanti, P. & Talotta, D. 1994), before antibodies appear. The presence of hepatitis C antibodies indicates exposure to the disease only. False positive results occasionally appear, however diagnosis can be further verified using ELISA (enzyme-linked immunosorbent assay) (M'Omish, F. et al. 1994). This assay detects antibodies to specific viral proteins. PCR (polymerase chain reaction) another confirmatory test, investigates the presence of genomic material (RNA). There has been increased refinement in testing procedures in the period 1994 – 1996, leading to detection of the virus within 14 days of exposure and higher specificity and sensitivity. A negative result, however, does not indicate an absence of HCV, as some people (~ 4%, Nakagiri et al, 1993), are only intermittently antibody positive (Steven, I.D. et al 1994).

1.1.4 Prognosis.

Cirrhosis of the liver, an end stage complication of chronic hepatitis C, is characterised by large and small degenerative nodules that are encased in scar tissue. Interspersed with these are normal liver parenchyma. Approximately 75% of cases of cirrhosis prove fatal within 1 - 5 years (Price & Wilson, 1982). Pathological changes progress slowly with only minor clinical symptoms until the major and late manifestations of the disease develop. These include: jaundice, peripheral oedema, bleeding disorders, hepatic encephalopathy, splenomegaly and oesophageal and gastric varices (Price & Wilson,

1982). In all cases, these symptoms are life threatening and can only be treated palliatively, at great expense to the community. There is no treatment to reverse the development of the fibrotic nodules, other than liver transplantation.

Hepatitis C is also closely linked with the development of hepatocellular carcinoma. While hepatitis C has not been proven to be directly carcinogenic, studies indicate that there is significant malignant transformation in the form of chronic necroinflammatory hepatic disease, (as in the case of cirrhosis), that leads to the formation of carcinogenic tumours (Kew, M.C. 1994). Cancerous cells tend to compress the surrounding normal liver tissue and spread quickly via invasion of the portal vein. Haemorrhage and cell destruction are major complications of hepatic carcinoma. Otherwise, progression of the disease may be asymptomatic.

Iwarson describes the outcomes of exposure to Hepatitis C in the following diagram;

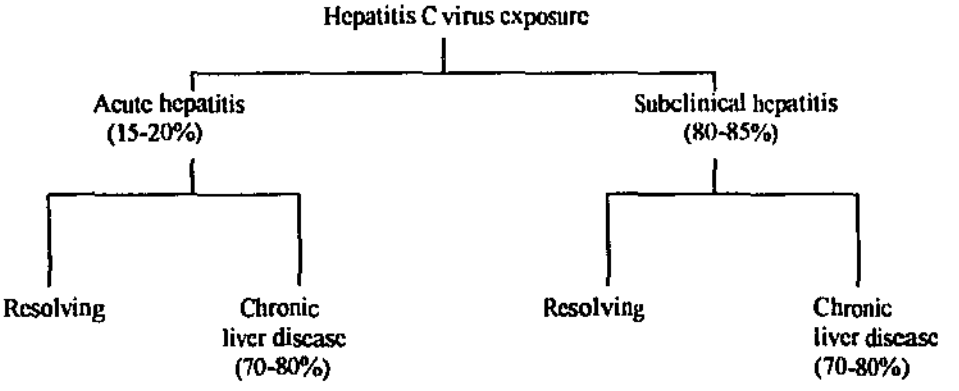

Figure 2. The outcome of hepatitis C virus exposure.

1.2 Prevalence.

1.2.1 Geographical distribution.

As stated previously, hepatitis C has eleven distinct genomic types known to date. These are Types 1 to 11 with subgroups a, b, and c . The eleven major genomes have discrete nucleotide sequences in the 5'-Non-Coding Region of the virus (M^{c}Omish, F. et al. 1994), that allow identification from DNA amplification and PCR testing. Improvements in testing procedures has greatly increased the ability to reliably differentiate, using standard tests, between the subgroups of each genomic type. As the virus continues to evolve, it is possible more genotypes will be identified.

In a study undertaken by M^{c}Omish and colleagues, 1994, 447 samples from nine different countries were examined, in an attempt to plot the global distribution of different genome groups. The participating countries were: Scotland, Finland, The Netherlands, Australia (Perth), Egypt, Hungary, Japan, Taiwan and Hong Kong. The table below shows the results of the investigation.

Country	No. of	Number & percent of donor samples of HCV genotype					
	Samples[a]	1	2	3	4	5	6
Scotland	144	67 (47%)	21 (14%)	56 (39%)	0	0	0
Australia	24	12(50%)	3 (13%)	8 (33%)	0	1 (4%)	0
Finland	12	3 (25%)	5 (42%)	4 (33%)	0	0	0
The Netherlands	31	18 (58%)	7 (23%)	5 (16%)	1 (3%)	0	0
Hungary	47	46 (98%)	0	0	1 (2%)	0	0
Egypt	19[b]	0	0	0	17(90%)	0	0
Taiwan	93	53 (57%)	40 (43%)	0	0	0	0
Japan	40	31 (77%)	9 (23%)	0	0	0	0
Hong Kong	37[c]	22 (59%)	1 (3%)	0	0	0	12(32%)
Total	447	252	86	73	19	1	12

Table 1. Prevalence of HCV types in different donor populations

[a] Number of PCR-positive samples typed by Restriction Fragment Length Polymorphism (RFLP)

[b] Two donors were infected with variants that could not be classified as type 1 to 6

[c] Two donors showed evidence of mixed infection with types 1 and 6

Table 1 illustrates that the predominant genotype in Perth, Western Australia is type 1, comprising 50% of the samples tested. Proportional incidence of types 2 and 3 are 13% and 33% respectively. The significance of the proportions of the genotype mix will be dealt with when discussing treatment of hepatitis C.

A study by Lin et. al., (1996), investigated response rates to α-Interferon among two hundred and thirty hepatitis C sufferers. This study represents one of the first studies to investigate genotype spread in Australia. Thirty-two of sixty-five subjects were previous injecting drug users. Other transmission factors included occupational exposure (3%, n=2), blood transfusion (32%, n=21) and unidentified exposure (16%, n=10). Twenty-four subjects were found to have type 1 hepatitis C, 38 type 3 and 3 were found to have mixed type 1 and 3 hepatitis C.

1.2.2 Transmission.

While the major transmission mode for hepatitis C is parenteral in up to half the reported cases the mode of transmission remains unknown (Maddrey, W.C. 1994). Thus, intravenous drug users and recipients of blood transfusions, prior to 1990, comprise the two major known risk groups. Smaller risk groups include male homosexuals and sex industry workers (Steven, I.D. et al 1994). Injecting drug users comprise the major risk group. A number of surveys have established the prevalence of HCV among intravenous drug users to be higher than 70% (Van Beek, I. et al. 1994). Some studies have found infection rates of 100%. Current data suggests the modal infection route comes from the sharing of injecting equipment (Steven, I.D. et al 1994).

Transmission of hepatitis C via blood transfusions was a primary source of infection, prior to the development of accurate screening techniques in 1990. Due to the mildness of specific presenting symptoms, and the high percentage of asymptomatic carriers, the true number of those infected with hepatitis C from blood transfusions did not become apparent until after 1988. The Centre for Disease Control (USA) now estimates 150,000 or more acute HCV infections each year (Maddrey, W.C. 1994). The rate of infection via blood transfusion has declined since 1990, as blood products undergo heat treatment to destroy the virus. Prothrombin (a clotting factor) is unable to undergo this preventive measure, (Steven, I.D. et al 1994), which still leaves Haemophiliacs at risk of infection. By 2002, the Australian Red Cross Blood Service estimated the risk of contracting hepatitis C via a transfusion as 1 in 330,000 units transfused.

There have been some studies that support the significance of sexual transmission of the virus (Gabrielli, C et al. 1994, Sato, B., et al 1994). The establishment of a proportional rate of infection has not been established, but is thought to be in the region of 5% (Maddrey, W.C. 1994). Coupled with the sexual mode of transmission is evidence of a higher rate of transmission among those already infected with either the hepatitis B and/or HIV/AIDS virus (Gabrielli, C et al. 1994, Sato, B., et al 1994, Van Beek, I. et al. 1994) with those working in the sex industry without adequate protection most likely to acquire the virus through sexual transmission (Nakashima, K., et. al 1992). The pie chart below, adapted from Maddrey 1994, illustrates transmission modes of the hepatitis C virus.

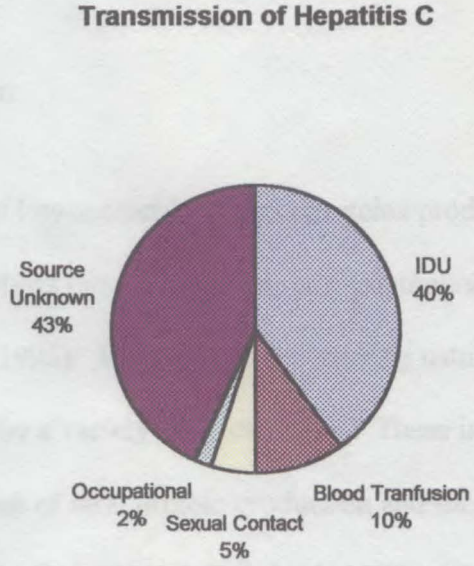

Figure 3. Transmission modes of hepatitis C, adapted from Maddrey (1994)

There are three other minor methods of contracting the hepatitis C virus. Organ transplant recipients are at risk. However, all donors are screened for HCV and the risk is minimal. Foetal infection has not been substantiated, although there does appear to be a higher incidence among mothers that are both HIV and HCV antibody positive. Health care workers are another group of people that are at risk of exposure, primarily through needle-stick injury. The rate of infection is lower with hepatitis C than with hepatitis B, and is estimated to represent 2-3% of the total population of those infected (Steven, I.D. et al 1994).

1.3 Treatment.

1.3.1 Alpha-2b-Interferon

Interferons are a group of low-molecular weight proteins produced by leukocytes (interferon alpha), fibroblasts (interferon beta), and T-lymphocytes (interferon gamma) (Zein, N.N & Rakela, J. 1995). These proteins occurring naturally in humans have an anti-viral effect, utilised by a variety of mechanisms. These include the inhibition of viral replication, inhibition of viral protein production and the prevention of virions release from infected cells (Zein, N.N & Rakela, J. 1995). Highly purified interferons were made available for public consumption following the introduction of recombinant DNA technology.

There are three commercially available types of interferons. Two of them are recombinant interferons, interferon alpha-2a and interferon alpha-2b, while the third is a naturally occurring interferon, interferon alpha-NL (Zein, N.N & Rakela, J. 1995).

Due to the high percentage of people with an absence of clinical signs it is often difficult to institute α-Interferon therapy in the early stages of the disease. Where inflammation of the liver is detected, it is recommended that treatment begin. Those patients with advanced cirrhosis and major neuropsychological symptoms are not appropriate candidates for α-interferon therapy (Maddrey, W.C. 1994).

Treatment of acute-phase hepatitis C infection with α-interferon has produced initial evidence that it may prevent progression to chronic hepatitis C. It must be

emphasised that this evidence is not conclusive due to small sample sizes and the varying dosages used in each study (Zein, N.N & Rakela, J. 1995).

Alpha-interferon is the medication of choice in the treatment of chronic hepatitis C. The generally accepted regime involves the administration of 3 million units, by injection, three times a week for twenty-four weeks (Hantz, O., Turin, F. and Trepo, C. 1993, Maddrey, W.C. 1994, Schiff, E.R. 1993, Zein, N.N & Rakela, J. 1995). Studies have shown that only 50% of those treated respond, with a return to normal alanine aminotransferase treatment (ALT) levels, after six months of therapy. Only 25% of these maintain a sustained recovery (Maddrey, W.C. 1994, Zein, N.N & Rakela, J. 1995), with females and younger persons experiencing better responses to treatment. The reasons why a sustained response is not maintained are not completely clear, although factors that influence the response to interferon therapy have been identified.

a) Age and gender: A study by Causse et al, demonstrated an independent positive correlation with female sex ($P<0.03$) and younger age ($P<0.05$) (Zein, N.N & Rakela, J. 1995). Hantz, Turin and Trepo (1993) also indicate younger age as an indicator for enhanced response to interferon therapy.

b) Dosage and duration of therapy: Studies are still progressing in an effort to identify a regime that will produce maximum benefit, combined with minimum side effects. Currently optimal dosage and duration of therapy have not been established, and a more effective regime than 3 million units, three times a week, for twenty-four weeks, may be identified.

c) Type of interferon: There has been very little investigation into the effectiveness of the different types of interferons available. A study by C. Cimino et al, (1992, cited in Zein et al, 1995), identified ten patients who, after not responding to the recommended treatment with interferon alpha-2a, were then treated with lymphoblastoid interferon 6 million units, three times a week for 2 months, followed by a reduction to 3 million units, three times a week for 4 months. Five of the recipients showed a return to normal ALT levels at the end of the treatment (Zein, N.N & Rakela, J. 1995).

d) Liver Histology: Biopsy of the liver, prior to interferon therapy, allows a precise measurement of the progression of chronicity. As the disease proceeds healthy liver tissue is replaced with scarred and fibrotic tissue. Studies have shown that patients with little or no fibrosis responded to therapy significantly better than those with severe hepatic disease. A summary of these studies shows that the rate of sustained response to therapy is greater in those patients with only mild hepatitis compared to those with active disease, evidenced by fibrosis or cirrhosis. Those with cirrhosis have the least likely response to interferon treatment (Zein, N.N & Rakela, J. 1995).

e) Serum HCV RNA level: Blood sampling to measure the level of hepatitis C virus RNA levels prior to the commencement of interferon therapy, appears to be a useful predictor of responsiveness to the treatment. Those people with significantly lower titre levels were more likely to be long-term responders. It is interesting to note that in a study by Hagiwara and associates, higher titre levels corresponded with those patients with advanced liver disease, following biopsy (Zein, N.N & Rakela, J. 1995).

f) HCV genotype: Studies have shown that partial or complete short-term biochemical response to interferon was demonstrated in 55% of patients with HCV type 1b, whereas, an 89% response rate was identified with patients of other types, primarily type 2a, 2b and type 3. A statistically significant difference of P=0.01 was demonstrated. These studies however are still preliminary, and there is some conjecture that mutation of the viral RNA is the cause of resistance to therapy (Zein, N.N & Rakela, J. 1995).

A list of the side effects of interferon therapy are listed below along with the percentage of patients experiencing them. (Zein, N.N & Rakela, J. 1995). It should be noted that some of the side effect are quite severe and may require extreme and long term medical support in their own right.

Side effects	Percent of Patients (%)
Flu-like syndrome Fever, headache, chills, myalgia, fatigue	60-80
Bone marrow hypoplasia Anaemia, leucopoenia, thrombocytopenia	<5
Cardiovascular disorders Arrhythmia, cardiomyopathy, hypertension	<5
Endocrine disorders Exacerbation of diabetes mellitus, thyroid, gynecomastia	<5
Gastrointestinal disorders Taste alteration, anorexia, diarrhoea	15-25
Liver and biliary Jaundice, autoimmune hepatitis, hepatic failure/ encephalopathy	<5

Table 2. Side effects of Interferon treatment.

Two other problems exist with therapy involving interferons. The treatment is very expensive, ranging from $33,000 to $70,000 per course of treatment, dependent on the

severity of the disease at the commencement of treatment (Sheill, A. et al. 1994). Finally, interferon must be administered subcutaneously. In most cases this involves visiting the doctor or hospital three times a week, causing inconvenience and added cost.

INJECTING DRUG USE: TRANSMISSION, PREVALENCE RATES AND PRACTICES.

This chapter undertakes a full review of Australian studies examining transmission modes, prevalence rates and injecting drug use practices of intravenous drug users. The review is undertaken in chronological order.

2.1 Transmission Modes.

Intravenous drug users (IVDU's) comprise the major population group at risk of contracting hepatitis C (HCV). Transmission occurs primarily through the sharing of needles and injecting equipment, including spoons, filters and water. Studies conducted in Australia have shown transmission rates among injecting drug users to be dependent on duration of injecting drug use, age and frequency of needle sharing. To a lesser extent opiate users are more likely than stimulant injectors to have contracted the virus as are those previously exposed to hepatitis B and heterosexual IVDU's rather than homosexual IVDU's (van Beek et al. 1994).

Kaldor et al., (1992) estimated risk factors for hepatitis C from a cohort of blood donors in Sydney over a fourteen month period. Injecting drug use was identified as the major risk factor in 47.7% of HCV infections, with a relative risk (estimated as an odds ratio) of 63 (95% confidence interval, 19-260). Other significant transmission factors include tattoos (40%), more than one lifetime sexual partner (9.1%), a previous sexually transmitted disease (30%) and time spent in prison (12.3%). The authors discuss the limits associated with their findings, including a self-report method that may have introduced bias, but many of their findings have been supported elsewhere (Waddell, R.G. 1994; van Beek et al. 1994; Croft, N et al. 1993; Crofts N. et al. 1995). Table 3

shows the significant risk factors associated with HCV transmission identified in this study.

Risk Factor*	Cases (%) responding yes to survey	Relative Risk (95% confidence Interval)	2-tailed P value
Injecting Drug Use	105(47.7%)	63(19-260)	<0.00001
Tattoo	67(30.4%)	11(4.9-26)	<0.00001
More than one lifetime sexual partner	88(40.0%)	7.2(4.1-13)	<0.0001
Sexually transmissible disease+	66(30.0%)	4.6(2.5-8.4)	<0.0001
Hepatitis-like symptoms	36(16.4%)	4.9(2.1-12)	<0.0001
Hepatitis contacts++	56(25.4%)	2.1(1.3-3.6)	0.0024
Prison inmate	27(12.3%)	14(3.3-91)	<0.0001
Institution resident+++	38(17.3%)	2.9(1.4-4.6)	0.00075

Table 3. Significant risk factor associated with HCV transmission among blood donors (Kaldor et al. 1992).

* items not mutually exclusive
+ Syphilis, gonorrhoea, genital herpes, genital warts, non-specific urethritis.
++ Sexual or familial contact with a person who had hepatitis
+++ Armed forces, hospital, boarding school, children's home

2.2 Prevalence Rates.

One of the earliest studies on the prevalence of hepatitis C among Australian intravenous drug users was undertaken by Bell and associates in 1990. At a time when diagnostic testing of hepatitis C was in its infancy, 172 intravenous drug users had their blood tested for HCV antibodies comparing prevalence rates against duration of drug use. Infectivity increased markedly as length of drug used increased (see Table 4).

Bell et al. concluded that the odds of being HCV seronegative decreased by a multiplicative factor of 0.55 (95%C.I. 0.32 to 0.96) for each additional two years of intravenous drug use.

Anti-HCV status	Men (n)	Wome n (n)	Total (n)	Age (years)	Duration of injecting drug use (months)
Seropositive	99	49	148	25.6±4.0	63±36
Seronegative	13	11	24	24.9±5.1	37±25

Table 4. Comparison of anti-HCV seropositive and seronegative groups. (Bell et al, 1990)

Desland and Batey (1991) reported mean ages of first injecting from two study groups in Sydney, New South Wales. Participants recruited from a Court Diversion program reported a mean age of first injecting of 14.0 years (SD 3.7 years) while those from a self-referred group had a mean age of 16.3 years (SD 4.7 years).

In a study of injecting drug users in Victoria (Crofts et al. 1993), 303 men and women were tested for the presence of HCV antibodies. Results for those testing positive are given as; a) duration of injecting drug use by age at interview (Table 5) and b) an odds ratio model after adjusting for age and duration of injecting (Table 6).

Duration of injecting years	Percentage of injecting drug users (n) <25 years	25-29 years	30-34 years	35+ years	Total
Men					
0-4	37%(38)	25%(8)	67%(3)	0(2)	37%(51)
5-9	67%(18)	63%(19)	67%(9)	100%(2)	67%(48)
10-14	-	100%(17)	93%(14)	100%(8)	90%(39)
15+	-	100%(45)	100%(16)	90%(28)	93%(45)
Total	**46%(56)**	**64%(45)**	**88%(42)**	**90%(40)**	**70%(183)**
Women					
0-4	35%(40)	60%(5)	0(4)	100%(1)	40%(50)
5-9	75%(16)	70%(10)	100%(2)	100%(3)	77%(31)
10-14	-	100%(12)	83%(6)	67%(3)	90%(21)
15+	-	100%(1)	70%(10)	100%(7)	83%(18)
Total	**46%(56)**	**82%(28)**	**73%(22)**	**93%(14)**	**65%(120)**
Total	**46%(112)**	**71%(73)**	**83%(64)**	**91%(54)**	**68%(303)**

Table 5. Percentage of injecting drug users seropositive for hepatitis C virus, by sex, age at interview and duration of injecting (Crofts et al. 1993).

Variable	Number positive (%)	Odds ratio	95% CI
Men(n=183)			
Sexual orientation			
Heterosexual	157(69%)	1.0	
Bi/Homosexual	21(59%)	0.62	0.2-1.8
Current primary drug			
Non-opiate	43(33%)	1.0	
Opiate	133(77%)	4.48	1.9-1.6
First injected drug Non-opiate	85(49%)	1.0	
Opiate	99(83%)	3.45	1.6-7.6
Prison history No	106(55%)	1.0	
Yes	85(82%)	2.30	1.0-5.4
Methadone history			
No	110(55%)	1.0	
Yes	81(84%)	2.94	1.2-7.3
Currently on methadone			
No	147(60%)	1.0	
Yes	44(91%)	4.32	0.9-9.5
Region			
Metropolitan	164(67%)	1.0	
Rural	27(70%)	0.56	0.2-1.6
Women (n=120)			
Sexual orientation			
Heterosexual	88(67%)	1.0	
Bi/Homosexual	35(53%)	0.81	0.2-2.6
Current primary drug			
Non-opiate	24(44%)	1.0	
Opiate	93(68%)	2.57	0.9-7.5
First injected drug			
Non-opiate	65(59%)	1.0	
Opiate	55(66%)	0.49	0.2-1.3
Prison history			
No	107(59%)	1.0	
Yes	17(88%)	3.08	0.6-5.6
Methadone history			
No	77(49%)	1.0	
Yes	47(85%)	6.80	2.1-2.1
Currently on methadone			
No	94(56%)	1.0	
Yes	30(83%)	6.35	1.4-9.7
Region			
Metropolitan	107(63%)	1.0	
Rural	17(65%)	0.51	0.1-1.9

Table 6. Percentage of male and female intravenous drug users who were HCV seropositive, and odds ratios for seropositivity after adjusting for age and duration of injecting (Crofts et al. 1993).

Men with a prison history, who used an opiate either as current primary drug or first injected drug, and who had a history of methadone or other drug treatment were more likely to have contracted HCV. For women a significant association was found with a methadone history, and a marginal association with current opiate use. Contrary to the findings for the men a negative marginal association was found among females for use of an opiate as first drug injected.

Waddell, 1994, tested 989 injecting drug users presenting to a sexually transmitted disease clinic in South Australia. He identified a transmission rate of 29.6% (males, 26%, females, 36%), with a follow up of 696 individuals. Two people serconverted giving an incidence of HCV infection of 3.5 per 100 person-years (95% confidence interval (0.4-12.7 per 100 person-years). In contrast to the Kaldor study there were a higher percentage of amphetamine and occasional injecting drug users than opiate users in this study.

One of the most comprehensive investigations into the transmission of HCV among injecting drug users was conducted by van Beek et al. in 1994. Two hundred and one known injecting drug users attending the Kirketon Road Centre in Sydney were tested for HCV antibodies. Characteristics of injecting drug use and their association with HCV transmission are summarised in Table 7.

Characteristic	Number	HCV prevalence (%)	95% CI	p-value*
Sex:				
Male	94	55	45-65	
Female	107	63	53-72	0.3
Age Group:				
15-19	30	17	3.3-30	
20-24	65	51	39-63	
25-29	44	70	57-84	
30-34	33	70	54-85	
35+	29	93	84-100	<0.001
Years since first injecting:				
<3	50	26	14-38	
3-6	29	38	20-56	
6-10	34	62	45-78	
10+	36	94	87-100	
Unknown	52	77	66-88	<0.001
Frequency of injecting:				
Occasional	48	40	26-53	
Regular	130	67	59-75	
Unknown	23	57	36-77	0.004
Drugs injected:				
Stimulants only	37	22	8.4-35	
Opiates only	70	74	52-74	
Both	76	63	52-74	
Unknown	18	61	39-84	<0.001
Sharing of equipment:				
Never	40	38	22-53	
Ever	147	65	57-72	
Unknown	14	36	39-89	0.003
Sexual practice:				
Homosexual	20	35	14-56	
Bisexual	41	56	41-71	
Heterosexual	107	70	61-79	
Unknown	33	42	26-59	<0.001
Involvement in sex industry:				
No	107	62	52-71	
Yes	94	56	46-66	0.54
HIV positive:				
No	180	60	53-67	
Yes	14	57	31-83	
Unknown	7	43	6.2-80	0.66
HBV Infection:				
Unexposed	103	42	32-51	
Exposed	95	78	70-86	
Unknown	3	67	13-100	<0.001

Table 7. Univariate analyses of HCV prevalence among 201 IDUs attending Kirketon Road Centre (van Beek et al. 1994).

*p value = the significance of the difference in HCV prevalence between the levels of the factor indicated.

Age was significantly associated with HCV prevalence ($p<0.001$) as was length of injecting drug use, frequency of drug use, opiate use, sharing of injecting drug equipment and heterosexual practices. Those working in the sex industry had a slightly lower HCV prevalence than those not, 56% vs. 62%, though this difference failed to reach statistical significance. Exposure to hepatitis B was strongly associated with HCV (78% exposed vs. 42% unexposed ($p < 0.001$)).

Characteristic	Odds Ratio	95% Confidence Interval	p-value*
Years since first injecting			
<3	1.0		
3-6	1.1	0.34-3.8	
7-10	2.6	0.83-8.4	
10+	19.3	2.9-130	
Unknown	7.5	2.1-27	0.001
Drug injected			
Stimulants only	1.0		
Heroin only	5.9	1.8-19	
Both	5.5	1.7-17	
Unknown	3.4	0.64-18	0.011
Sexual practice			
Homosexual	1.0		
Bisexual	3.3	0.76-14	
Heterosexual	4.9	1.3-19	
Unknown	1.4	0.32-6.4	0.026
Age			
15-19	1.0		
20-24	4.5	1.2-16	
25-29	5.0	1.2-20	
30-34	3.5	0.72-16	
35+	12.7	1.5-105	0.064
Frequency of injecting			
Occasional	1.0		
Regular	1.7	0.67-4.7	
Unknown	1.0	0.22-4.4	0.458

Table 8. Multivariate logistic analyses of HCV prevalence among IDUs attending Kirketon Road Centre (van Beek et al. 1994).

*p value = the significance of the difference in HCV prevalence between the levels of the factor indicated, when all other factors in the table are included in the logistic model.

Multivariate analysis using logistic regression (Table 8), showed significant factors involved in HCV transmission to include years since first injecting, drug injected sexual practice, age and frequency of injecting.

Nick Crofts, in 1994, examined the magnitude of the hepatitis C epidemic and its implications for future health planning. In this editorial he states;

"Almost every population of IDU's so far studied has shown very high prevalences of exposure to HCV: 90% and more among entrants to methadone programmes, 30-70% in field recruited and clinic samples in the West. There are indications of even higher rates of HCV infection among IDU's in South-east Asia and South America. Risks begin with the first injection, and in some populations rates of exposure as high as 40% has occurred within 2 years of beginning to inject. By the time IDU's have been injecting for several years, their chances of having been exposed to HCV approach 100%. High incidences have also been observed: 20% p.a. in a cohort in Australia, and 10% p.a. in a cohort in the Netherlands. It is estimated that there are as many as 10,000 or more new HCV infections per year as a result of IDU in Australia."

Crofts et al., 1995, conducted a one year study of all prison entrants in Victoria. A total of 3,627 men and women (>99% of all entrants), were tested for hepatitis B and C antibodies and HIV antibodies. Of the sample, 1,561 (43%) were injecting drug users. The prevalence rate among this group was 65.3%, with injecting drug using women having the highest seroprevalence. Table 9 shows the prevalence of HCV antibodies in Victorian prisons by gender.

Detail	Users of injecting drugs	No use of injecting drugs	Odds ratio (95% confidence interval)
Men:			
No. by drug use*	1436	1749	
Mean (SD) age(years)	26.8 (6.8)	31.5(10.2)***	
No.(%) anti-HCV pos	897/1,410 (63.6)	274/1,712 (16.0)	9.15 (7.7 to 0.9)***
Women:			
No. by drug use*	125	54	
Mean (SD) age(years)	26.8 (6.1)	32.7 (10.6)***	
No.(%) anti-HCV pos	100/118 (84.8)	14/53 (26.4)	15.50 (6.5to37.5)***
All men and women:	1561	1803	
Mean (SD) age(years)	26.8 (6.5)	31.6 (10.2)	
No.(%) anti-HCV pos	997/1,528 (65.3)	288/1,765 (16.3)	9.61 (8.1 to 11.4)***

Table 9. HCV antibody prevalence in prison entrants in Victoria, Australia, according to use of injecting drugs, October 1991 to September 1992. (Croft, N. et al. 1995).

*Drug use not known for 242 men and 18 women *** P< 0.001

For the duration of the study, 312 entrants were readmitted to prison. These people were re-tested. Estimates were calculated for incidence per 100 person years at 38.2 (Confidence interval: 19.1 to 76.4) for injecting drug users (see Table 10).

Detail	No. initially sero-negative	No. of sero-converters	Mean (SD) period of observation days	Range of observation days	Incidence rate per 100 person years (95% confidence interval)
Drug users	47	8	163 (89)	3-348	38.2 (19.1 to 76.4)
Non drug users	72	2	171 (89)	4-339	5.9 (1.5 to 23.6)
Total	119	10	168 (89)	3-348	18.3 (9.8 to 34.0)

Table 10. Incidence of infection with hepatitis C virus among subjects entering prison more than once, October 1991 to September 1992. (Crofts, N et al. 1995).

The National Centre for Research into the Prevention of Drug Abuse, Curtin University of Technology, has conducted several studies on injecting drug use in Perth, Western Australia between 1994 and 1997. Carruthers and Loxley, 1994, investigated the prevalence of HCV among young injecting drug users, age 12 to 20 (n=234). The prevalence rate of HCV among this young cohort was 5.5% (n=6 of 109 tested). Characteristics of those positive can be seen in Table 11.

One significant limitation of this study resulted from the method of blood collection for HCV testing. Finger-prick collection was noted to be difficult due to clotting of blood and in transferring the blood from the thumb to the tube. Revisions of collection techniques were instituted, however the initial problems may have resulted in the low proportion of samples taken (46%) compared to the questionnaire sample. The prevalence rate for this sample may be higher than 5.5%.

Characteristic	Number
Gender:	
Male	3
Female	3
Age:	
15 years	1
16 years	1
18 years	2
19 years	1
20 years	1
Aboriginal:	
Yes	1
No	5
Injecting?:	
Yes	6
No	0
Drug used most often	
Heroin/Homebake	2
Speed	1
Tranquillisers	1
Alcohol	2
High Risk Behaviour Score(/30)	
1	1
4	1
6	2
8	1
10	1
Risky Piercing	1
Risky Tattooing	0
Duration of injecting:	
less than one year	4
three years	2
Heard of HCV:	
Yes	4
No	2
Preferred Drugs:	
Heroin	2
Ecstasy	1
Amphetamine	2
Tranquillisers	1

Table 11. Characteristics of HCV Positive Respondents (n=6) (Carruthers and Loxley, 1994).

The 1996 Report of the Australian Study of HIV and Injecting Drug Use (ASHIDU), Bevan, Loxley and Carruthers, provides a comprehensive examination of injecting drug use behaviours and prevalence of blood-borne viruses (HBV, HCV and HIV) in a group of 220 recruits in Perth, Western Australia.

Characteristic	n per group	%	χ^2	p
Age Group	185		72.9	<0.001
Up to 20	46	15.2		
21 to 25	42	16.7		
26 to 30	31	25.8		
31 to 35	30	73.3		
36 years +	36	88.9		
Treatment	179		36.8	<0.001
Never	66	12.1		
Ever	113	58.4		
Age/Treatment	179		59.5	<0.001
Young/never	47	6.4		
Young/ever	36	27.8		
Older/never	19	26.3		
Older/ever	77	72.7		
Last drug injected	165		13.6	0.001
Amphetamines	81	27.2		
Opioid	75	56		
Other drug	9	33.3		
Duration of IDU	185		73.9	<0.001
0-4 years	63	11.1		
5-9 years	51	25.5		
10-14 years	21	61.9		
15 years +	50	86.0		

Table 12. HCV reactive serology by age, treatment, age/treatment, last drug injected and duration of injecting drug use. (Bevan, Loxley and Carruthers, 1996).

The average age of respondents was 27.5 years, standard deviation 7.5 years, range 14 to 47 years. Males comprised 68.6% (n=151) of the study group. Blood samples for HCV testing was collected from 185 respondents, with 7 not supplying blood and 28 supplying a sample insufficient for testing. Of the 185 respondents tested, 76 were HCV antibody

positive, a prevalence rate of 41.1%, 95% confidence intervals 37.48% to 44.72%. Characteristics of those testing positive for HCV antibodies are listed in Table 12. Chi-squared testing was performed and significant results listed.

Variables associated with HCV status include: age of the injecting drug user, with the higher proportion of those hepatitis C positive in the older age groups; having ever been in a treatment group (for example a Methadone programme); combined age-treatment groups with young/ever more likely to be reactive to HCV than young/never and older/ever more likely to be HCV reactive than older/never; amphetamine users less likely to be HCV reactive than opioid users and duration of injecting drug use. Age and length of injecting drug use were highly correlated, $r = 0.88$ (Bevan, Loxley and Carruthers, 1996).

Hando et al (1997) profiled the demographic, drug use and criminal correlates of 279 youths detained in New South Wales Juvenile Justice Centres. A quarter of the sample (24%) had injected an illicit drug. Three-quarters (77%) of those who had used heroin and two-thirds (64%) of those who had used amphetamines had injected those substances. One-third (37%) of those who had injected reported using a needle before or after someone else had used it, and 18% reported doing so in the month before detention. Over half (58%) of those who had shared needles in the past month did not always clean them.

Crofts and Aitken (1997) assessed the incidence of blood-borne infection among a cohort of injecting drug users over the period 1990 to 1995. Annual hepatitis C prevalence rates

among this cohort ranged from 81% in 1990 to 69.6% in 1995 (lowest rate, 67.7% in 1993), although it is not clear if all participants were tested each year. Incidence rates were also calculated and are given below.

	1990-1991	1992-1993	1994-1995	Overall
hepatitis C virus				
Seroconverters	5	8	6	19
Person-years at risk	30.1	73.4	74.1	177.6
Incidence (per 100 py)	16.6	10.9	8.1	10.7
95% CI	6.9-40.0	5.5-21.8	3.6-18.0	6.8-16.8

Table 13. Biennial incidence of hepatitis C virus in a cohort of Victorian injecting drug users, 1990-1995. (Crofts and Aitken, 1997).

Loxley et al (1997) were investigators in the 1994 Australian Study of HIV and Injecting Drug Use (ASHIDU). Their paper reports age standardised infection rates of hepatitis C across four Australian cities. In Perth, Western Australia, the infection rate for males was 56.4% and for females 44.1%.

City	Men	95% CI	Women	95% CI
Adelaide	54.4	50.0-58.8	51.3	45.5-57.1
Melbourne	61.1	56.7-65.5	63.3	57.8-68.8
Perth	56.4	52.0-60.8	44.1	37.5-50.7
Sydney	73.1	69.2-77.0	68.4	62.8-74.0
National	**59.4**	**57.2-61.6**	**58.6**	**56.6-61.6**

Table 14. Age-standardised hepatitis C prevalences and confidence intervals, by city and gender (Loxley et al, 1997).

The Fitpack Study, (Lenton & Tan-Quigley, 1997), examines the injecting drug patterns and behaviours of recreational and occasional injecting drug users. This cohort traditionally have minimal contact with conventional drug treatments agencies and represent an unknown subgroup for this population. Accessed by questionnaire through

the sale of Fitpacks (needle and syringe packs), 513 responded, a response rate of 20%. Hepatitis C questions were self-report only, where 64.9% reported testing for HCV, with those positive for the virus 25.2%. While this rate is lower than the ASHIDU sample (Bevan, Loxley and Carruthers, 1996), mean length of lifetime injecting is correspondingly lower. Table 14 illustrates key variables associated with self-reported HCV testing.

	Positive HCV result (%)			
	No	Yes	n(1)	sig(2)
Under 26 years of age	60.5	14.9	292	0.0000
Females	46.6	38.1	275	0.2769
Are married or living with sex partner	47.0	52.0	295	0.5417
Have children	41.4	58.8	290	0.0143
Are employed	47.0	29.8	296	0.0135
Live in the city	87.8	84.6	245	0.6983
First injected at less than 18 years of age	46.1	41.7	286	0.6128
Less than 10 years of injecting	79.1	21.9	281	0.0000
Stimulants injected with this Fitpack	67.9	36.3	296	0.0000
Depressants injected with this Fitpack	43.0	82.2	296	0.0000
Injected stimulants in past month	76.8	46.1	296	0.0000
Injected depressants in past month	51.3	81.7	296	0.0000
Injected at least daily in past month	34.9	61.3	296	0.0001
Shared needles in past month	40.9	44.2	296	0.7246
Shared other equipment in past month	55.7	59.3	296	0.6864
Prior contact with specialist drug agency	55.4	29.6	289	0.0001
Have been charged with a drug offence	50.1	75.2	296	0.0003

Table 15. Self reported positive Hepatitis C result by key variables for those Hepatitis C tested: Percent respondents.

1) Each row represents 2 cells of a 2x2 contingency table and n is overall value for all 4 cells of the 2x2 table.

2) Chi-squared test corrected for continuity. Bonferroni adjustment was employed at an experiment wise error rate of 0.05 which set alpha for each comparison at 0.0029.

Those testing positive for HCV were more likely to have children, to have been charged with a drug offence and to have had contact with a specialist drug treatment agency. A positive HCV result was associated with having injected for 10 or more years, injecting depressants with the Fitpack and having had contact with a specialist drug treatment

agency. Length of duration of injecting drugs in predicting HCV positivity remained consistent with earlier research (Bevan, Loxley & Carruthers, 1996; van Beek et al. 1994). The Lenton study reports those respondents injecting for under 10 years had a self-report HCV positivity rate of 6.9% while for those injecting for 10 years or more, the rate was 52.5% (Lenton, S & Tan-Quigley, A. 1997).

	Fitpack (n=285)	Ashidu (n=140)
4 years or less	2.1%	7.9%
5-9 years	13.4%	30.8%
10-14 years	52.7%	55.6%
15+ years	52.4%	75.6%

Table 16. Percentage of respondents positive for hepatitis C by length of use. (Lenton, S & Tan-Quigley, A. 1997).

Lynskey and Hall (1998) examined changes in age of initiation to heroin use over time. They examined results of both the ANAIDUS and ASHIDU studies comparing age of initiation to heroin use with the respondent's decade of birth (see Table 16). While the mean change in age of initiation was not statistically significant there was a consistent decrease among heroin users born in later decades.

	Mean age at first heroin use					
	ANAIDUS			ASHIDU		
Decade of birth	Males	Females	Persons	Males	Females	Persons
1940-1949	20.1	20.5	20.2	26.1	26.0	26.1
1950-1959	18.4	17.6	18.2	20.2	20.8	20.3
1960-1969	16.7	17.5	17.0	19.4	20.5	19.8
1970-1979	14.8	14.7	14.7	17.5	17.5	17.5

Table 17. Mean age at first heroin use for respondents born in different decades. (Lynskey and Hall, 1998).

The National Centre in HIV Epidemiology and Clinical Research produces an Annual Surveillance Report on HIV/AIDS, Hepatitis C and Sexually Transmissible Infections in Australia. Nationally, more than 125,000 persons have been diagnosed with hepatitis C infections since 1990. Since 1994 the number of new cases has remained relatively stable at 18,000 to 20,000 per year. It is estimated that the number of known cases represents 60% of all cases of hepatitis C in Australia, based on duration and severity of disease and known efficacy of reporting systems (Annual Surveillance Report, 1999). Injecting drug use is the major transmission factor in 75% to 80% of all Australian cases. In Western Australia the number of newly diagnosed case of hepatitis C are as follows:

Year	Number of persons	Rate per 100,000 population (June 1996)
1994	1,314	74.4
1995	1,146	64.9
1996	1,146	64.9
1997	1,137	64.4
1998	1,261	71.4

Table 18. Number and rate of diagnosis of hepatitis C infections 1994-1998 for Western Australia. (Annual Surveillance Report, 1999).

Nationally, diagnosis of hepatitis C by age group and gender for1998 are as follows:

Age group (years)	Male	Female	Total*
0-4	69	60	133
5-14	25	21	46
15-19	724	659	1,401
20-29	3,416	2,239	5,738
30-39	3,823	2,270	6,136
40-49	2,521	1,129	3,673
50-59	393	221	619
60+	368	309	687
Not known	24	8	41
Total	11,363	6,916	18,474

Table 19. Number of diagnoses of hepatitis C infection, 1998, by age group and sex (Annual Surveillance Report, 1999).

*Totals include diagnoses in people whose sex was not reported.

Crofts et al (1999) compared transmission rates of hepatitis C and HIV among Australian intravenous drug users. They identified a prevalence rate of hepatitis C of 65% and estimated the incidence of new cases to be in the order of 6,000 to 10,000 per year across Australia for this group.

2.3 Incidence and Prognosisof Cirrhosis and hepatocellular carcinoma.

Crofts (1994) stated that the majority of persons exposed to hepatitis C become chronically infected.

"'Among an unknown proportion, there is an incubation period of 20-30 years to end-stage liver disease and in a smaller proportion to hepatocellular carcinoma."

In 1997, Alex Wodak summarised the incidence and prognosis of hepatitis C infected persons as follows:

"About 20% develop cirrhosis over a 20 year period of whom about 5% develop liver failure and another 5% liver cancer within 5 or more years. Complications of chronic hepatitis C infection will result in many patients requiring frequent hospitalization. Perhaps 50% of people with chronic hepatitis C develop a lingering illness with debilitating fatigue precluding employment and often home duties. Fatigue may be one of the most expensive aspects of the hepatitis C epidemic."

Yano et al (1994) quantified the survival rate of persons with hepatitis C induced cirrhosis. Ten years after being diagnosed with cirrhosis of the liver 62.3% were still alive, however, after fifteen years this number had decreased to 35.9%.

2.4 Injecting drug use practices.

There are many practices undertaken by injecting drug users that put them at risk of contracting blood-borne viruses. These include; the sharing of needles and other injecting equipment, unsafe sexual practices and high risk tattooing and body piercing. Other environmental factors that appear associated with an increased risk of contracting

hepatitis C include type of drug injected, participation in methadone programmes, incarceration and co-infection with hepatitis B and or the human immunodeficiency virus (HIV).

Ross et al (1993) compared needle sharing practices among respondents of the two ANAIDUS studies undertaken in 1989 and 1990. As different groups of respondents were sampled for each study, results here are a comparison of practices across time rather than across individuals.

Description	1989	1990
Number of times needles & syringes used before too worn to use again	2.9±3.1	1.9±2.3
% of times use new needles and syringes	73.5±26.2	84.8±21.8
% of times easy to get new needles and syringes	84.3±20.7	93.0±14.3
Number of times new needles & syringes obtained when using	65.6±102.3	37.4±62.2
% of time needles & syringes used after someone else	19.0±25.8	9.7±18.5
% of time needles & syringes used first then shared	50.9±32.4	38.2±35.8
Number of people accepted used needles & syringes from in past 6 months	1.8±6.6	0.9±3.9
Number of people who used a needles & syringe before it's discarded	2.0±4.2	1.2±1.1
Reasons for sharing		
Factor 1: Don't care when withdrawing or intoxicated	5.1±1.7	6.0±1.6
Factor 2: Unavailability of equipment	0.3±0.6	0.1±0.4
Factor 3: Belief that risk is low	0.5±0.7	0.2±0.5
Time since last used needles & syringes after someone else		
Never	19.4	31.0
Years	27.8	28.2
Months	30.2	27.3
Weeks	13.9	8.2
Days	8.6	5.3

Table 20. Comparison of needle sharing practices in the 1989 and 1990 ANAIDUS studies (Ross, Stowe, Wodak and Gold 1993).

There was a downward shift in the rate of needle sharing in the year between sampling with a corresponding increase in the use of new needles and syringes. Of concern is the 13.5% of respondents in 1990 who conceded sharing daily or weekly.

Studies conducted by the National Centre for Research into the Prevention of Drug Abuse, investigating the rate of needle sharing among injecting drug users, all utilise a common measuring instrument, the High Risk Behaviour Scale (HRBS). This six item questionnaire examines frequency of drug use in the last month, frequency of using a needle after someone else in the last month, number of people that used the needle previous to the respondent in the last month, frequency of cleaning needles that other people have used prior to re-use in the last month, frequency of the use of bleach after someone has used the needle prior to re-use in the last month and the frequency of someone using a needle after the respondent in the last month. Respondents are given the choice of six responses rated from 0 to 5, giving a possible total of 30.

Level of risk	% of injectors	Number
No risk (score = 0)	20.4	32
Low risk (score = 1- 2)	38.9	61
Moderate to high risk (score > 3)	40.8	64

No risk = no sharing in the past month
Low risk = shared once with one or no person in the last month
Moderate to high risk = shared more than once with more than one person in the past month.

Table 21. HRBS scores for injectors (ever injected) (n = 167) (Carruthers and Loxley, 1994).

One hundred and sixty seven respondents involved with The Hepatitis C and Young Drug Users Study (Carruthers & Loxley, 1994) completed the HRBS. Scores ranged from 0 to 24 with a mean score of 3.5 (sd = 5.36, 95% confidence interval 0 - 14.6). The

results were further subdivided into three groups, no risk (HRBS = 0), low risk (HRBS = 1 -2) and moderate to high risk (HRBS > 3).

Mean HRBS were significantly lower for amphetamine users when compared to heroin and homebake users ($F_1 = 5.93$; $p = 0.01$). Seventy three percent ($n=128$) of those who had ever injected illicit drugs reported sharing other injecting equipment in the preceding twelve months. These included spoons, filters, cups and glasses, the drug mix, tourniquets and swabs (Carruthers & Loxley, 1994).

Van Beek et al, (1994), reported on a number of behavioural characteristics of 201 injecting drug users in Sydney, New South Wales. Among occasional injectors, 40% were hepatitis C positive, while 67% of regular injectors were infected with the virus. When frequency of sharing injecting equipment was investigated, 38% of those who had never shared equipment were infected, as were 65% of those who had shared.

Two hundred and twenty respondents completed the HRBS in the ASHIDU study (Bevan, Loxley and Carruthers, 1996). The mean score was 3.1 (sd 3.8; range 0 to 20). Table 22 shows the frequency of responses for each question.

Sub-scale item	HRBS score	frequency	%
Number of times injected in the past month		220	
Hasn't injected	0	26	11.8
Once a week or less	1	70	31.8
More than once a week	2	91	41.4
Once a day	3	17	7.7
2-3 times a day	4	13	5.9
More than three times a day	5	3	1.4
Number of times used a needle after someone else in past month		220	
No times	0	185	84.1
One time	1	14	6.4
Two times	2	5	2.3
3-5 times	3	9	4.1
6-10 times	4	2	0.9
More than 10 times	5	3	1.4
Missing data		2	0.9
Number of different people used needle before you in past month		220	
None	0	185	84.1
One person	1	31	14.1
Two people	2	3	1.4
3-5 people	3	0	0.0
6-10 people	4	0	0.0
More than 10 people	5	0	0.0
Missing data		1	0.5
How often in the last month cleaned needles before reusing them		220	
Doesn't re-use	0	185	84.1
Every time	1	27	12.3
Often	2	2	0.9
Sometimes	3	1	0.5
Rarely	4	2	0.9
Never	5	3	1.4
How often in last month cleaned needles with bleach before re-using		220	
Doesn't re-use	0	185	84.1
Every time	1	15	6.8
Often	2	1	0.5
Sometimes	3	1	0.5
Rarely	4	0	0.0
Never	5	18	8.2
How many times in the last month has someone used a needle after you have used it.		220	
No times	0	186	84.5
One time	1	12	5.4
Two times	2	9	4.1
3-5 times	3	9	4.1
6-10 times	4	1	0.5
More than 10 times	5	0	0.0
Missing data		3	1.4

Table 22. Frequency and percentage of responses to questions comprising the HRBS Drug Uses sub Scale (Bevan, Loxley and Carruthers, 1996).

When questioned about sharing of needles at the last injecting occasion, 90.7% reported using a new needle with 7.2% reporting sharing of needles (Table 23).

	Frequency	Percentage %
Used new needles only	176	90.7
Used anothers needles		
Regular sexual partner	5	2.6
Close friend	3	1.5
Reused own needles		
Injected alone	4	2.1
Injected with one other	4	2.1
Injected with more than one other	2	1.0

Table 23. Self-reported re-use and sharing of needles on the last injecting occasion for respondents who had injected in the last month (n=194) (Bevan, Loxley and Carruthers, 1996).

The Youth, AIDS and Drugs Study (Loxley, 1997), reports a mean HRBS score of 4.1, range 0-29, sd 5.6. The respondents for this study were aged between 14 and 20 years of age and are therefore comparable to the 1994 Hepatitis C and Young Drug Users study (Carruthers and Loxley, 1994). Respondents were assessed for risk management strategies related to their injecting drug use. The results are summarised in Table 24.

	Frequency	Percentage
Accept used needles from no-one	35	44
Accept used needles from lover or friend only if bleached	12	15
Accept used needles only from lover	22	28
Accept used needles only from a lover or close friend	8	10
Unclear	2	3

Table 24. Risk management strategies for injecting: Injectors (n = 79) (Carruthers and Loxley, 1994).

The Fitpack study (Lenton & Tan-Quigley, 1997) analyses the HRBS scores calculated from this study against ASHIDU data using the Chi-squared test (Table 25). Subjects of the Fitpack study reported injecting, receiving a used needle and passing on a used needle more frequently than those in the ASHIDU study (Bevan, Loxley & Carruthers, 1996) and were more likely to have used a needle after a larger number of people.

Respondents were also asked the frequency of sharing other injecting equipment in the last month. Of the 510 responses only 41.5% reported never sharing equipment and nearly 245 sharing on ten or more occasions (Table 26). Logistic regression analysis demonstrates that those likely to share equipment are more than four times as likely to have an income less than $10, 000 and four times as likely to have shared needles in the past month.

Sub-scale item	% RESPONDENTS Fitpack	ASHIDU[1]	Sig.(p)[2]
Number of times injected in the past month			
Hasn't injected	3.1	11.8	0.0000.
Once a week or less[3]	21.1	31.8	
More than once a week but not daily	37.1	41.4	
Once a day	14.8	7.7	
2-3 times a day	16.7	5.9	
More than three times a day	7.3	1.4	
Number of times used a needle after someone else in past month			
No times	72.3	84.8	0.0000
One time	10.9	6.4	
Two times	7.0	2.3	
3-5 times	5.4	4.1	
6-10 times	1.3	0.9	
More than 10 times	3.1	1.4	
Number of different people used needle before you in past month			
None	72.9	84.5	0.0000
One person	15.6	14.2	
Two people	5.0	1.4	
3-5 people	3.7	0.0	
6-10 people	1.9	0.0	
More than 10 people	1.0	0.0	
How often in last month cleaned needles with bleach before re-using			
Doesn't re-use[4]	72.2	84.1	0.0000
Every time	6.8	6.8	
Often	1.7	0.5	
Sometimes	5.3	0.5	
Rarely	8.1	0.0	
Never[4]	5.7	8.2	
How many times in the last month has someone used a needle after you have used it.			
No times	68.4	85.7	0.0000
One time	10.2	5.5	
Two times	7.8	4.1	
3-5 times	8.0	4.1	
6-10 times	1.9	0.5	
More than 10 times	3.8	0.0	

Table 25. Comparison of HRBS scores Fitpack vs Perth ASHIDU. (Lenton & Tan-Quigley, 1997).

1) ASHIDU data is in Valid percent (excludes missing data)
2) Test is non parametric Chi squared. Where expected frequency less than 5 cells were collapsed.
3) Collapses two response categories in Fitpack
4) Estimated values as described above.

Number of times	Frequency	percentage %
Never	212	41.5
Once	30	5.8
Two times	33	6.6
3-5 times	79	15.5
6-10 times	34	6.8
More than 10 times	122	23.9
Total	510	100.0

Table 26. Times in past month respondent shared other injecting equipment (Lenton & Tan-Quigley, 1997).

Dolan et al (1998) described a mathematical model of HIV transmission in New South Wales prisons. Parameter estimations of the mean number of shared injections per injecting drug user inmate per week ranged between 0.13 and 0.41.

Crofts et al (1999) reported an incidence of hepatitis C of 4% to 11.9% per year among intravenous drug users who reported never sharing needles and 17% to 30.2% per year among those who did.

The 1999 Annual Surveillance report, in a survey of persons using needle and exchange programs reported rates of needle sharing at between 9% and 21% in 1997 and 10% and 29% in 1998.

Year		Male (%)	Female (%)	Total (%)
1997	Injecting less than three years	11	21	15
	Injecting more than three years	13	15	14
	Not reported	11	22	14
1998	Injecting less than three years	13	24	17
	Injecting more than three years	17	20	18
	Not reported	19	14	18

Table 27. Rate of needle sharing by duration of use and year of IDUs accessing needle and exchange programs. (1999 Annual Surveillance Report).

2.5 Transmission through needle sharing.

In 1993, Waddell reported prevalence rates of hepatitis C among clients attending a STD clinic in South Australia. Follow up testing was undertaken among 73 clients and an incidence rate of 3.5 per 100 person years (95% C.I. 0.4 to 12.7) was determined.

Crofts, Stewart, Hearne et al (1995) assessed the spread of bloodborne viruses among entrants to Victorian prisons over a twelve month period from 1991 until 1992. They calculated a hepatitis C seroconversion rate of 18.3 per 100 person years (95% C.I. 9.8 to 34.0) for the total sample (3429 males and 198 females). Among only those entrants identified as intravenous drug users the seroconversion rate was 38.2 per 100 person years (95% C.I. 19.1 to 76.4) and among those aged 30 years or less the incidence was 41.0 per 100 person years (95% C.I. 20.5 to 82.0).

Crofts and Aitken (1997) examined the incidence of hepatitis C and risk behaviours among a cohort of Victorian injecting drug users. Respondents were interviewed at least three times over a five year period (1990 to 1995) and were grouped according to reports of needle sharing or not at each interview. Results indicate that although 66 respondents

reported never sharing needles or syringes, 65% were hepatitis C positive, with two seroconverting over the study period. This led to speculation that the virus was being transmitted via other injecting equipment, for example, the sharing of water and swabs.

Reports of sharing of Needles and syringes	HCV status		Sero-converters	Person-years at risk	Incidence per 100 py (95%CI)
	-	+			
Half or more of all interviews (n=63)	14	49	6	35.5	16.9 (9.8-48.5)
Fewer than half of all interviews (n=73)	21	52	7	48.6	14.4 (6.0-24.0)
None (n=66)	23	43	2	46.4	4.3 (1.5-14.3)

Table 28. Hepatitis C virus prevalence and incidence among 202 injecting drug users interviewed three times or more, by levels of risk, 1990-1995 (Crofts and Aitken 1997).

In 1997 Crofts and colleagues investigated the epidemiology of hepatitis C infection among Australian injecting drug users.

By examining the prevalence and incidence rates of two independent studies they calculated hazard rates and mean times until infection for injecting drug users in New South Wales and Victoria. Little difference was observed in the mean time to infection between the two groups (approximately 7 years).

	Injecting drug use		Total	Mean time to infection (y) (95%CI)
	Started before 1987	Started since 1986		
Victoria				
Hazard rate (95%CI)	0.171	0.129	0.146 (0.126, 0.169)	6.9 (5.9, 7.9)
Rate ratio (95%CI)	1.32 (0.82, 2.14)			
Sydney				
Hazard rate (95%CI)	0.258	0.129	0.148 (0.115, 0.188)	6.8 (6.0, 8.7)
Rate ratio (95%CI)	1.56 (0.67, 3.28)			
Combined				
Hazard rate (95%CI)	0.178 (0.103, 0.159)	0.129 (0.133, 0.229)	0.147 (0.129, 0.166)	6.8 (6.0, 7.8)
Rate ratio (95%CI)	1.32 (0.82, 2.14)			

Table 29. Seroconversion hazard rates and means times to infection with HCV among injecting drug users in two independent studies in Victoria and Sydney (Crofts et al 1997).

Crofts, Aitken and Kaldor (1999) attempted to explain the vastly differing rates of transmission of HIV and hepatitis C among intravenous drug users by modelling the probability of infection as a function of an infectivity rate. While the authors acknowledged the estimates were crude results were as follows:

IVDU population prevalence rate (A)		62.4%
Carrier rates (B)		80%
Needlestick infection probability estimates (C)		
	High	10.0%
	Low	2.7%
Probability of infection (AxBxC)	High	4.9%
	Low	1.3%

The authors estimated a probability of infection with hepatitis C of between 1% and 5% for each needle sharing act.

THE MATHEMATICAL MODEL

3.1 Background to Mathematical Models.

Mathematical models related to infectious diseases in humans in the early 1990's concentrated in the main on modelling the transmission and spread of HIV/AIDS within one and two sex communities (Anderson and May, 1989; Castillo-Chavez, 1989; Comiskey, 1993; Comiskey et al. 1993). During this time, research on hepatitis C had focussed primarily on transmission rates and modes as described in Chapter 2. As more data became available researchers have begun to construct mathematical models to predict the long-term spread and effects of the disease.

Mather and Crofts (1999), constructed a computer simulation of a Markov model to account for the large number of parameters and high levels of variation associated with hepatitis C transmission among injecting drug users. Their examination of previous infectious disease models, such as influenza and measles, suggested a short disease interval where the individual was only infectious for the span of the disease, leading to complete recovery. At this stage the individual had either developed a long-lasting immunity or returned to a susceptible state, as in the case of influenza. Few models had examined disease processes, such as hepatitis C, where infection and illness are a long-term proposition, with decades long incubation periods and enduring infectious states after recovering from acute infection.

Mather and Crofts used a stochastic micro-population model that essential followed the history of distinct individuals. This was done by dividing their cohort into sub-

populations in order to define the parameters at a group level and allow controlled experimentation within each group. An example of such a group is a prison population, where the prevalence rate is distinct and who have different behavioural characteristics to other groups. The system was treated as a finite-state stochastic process, however as the time units were small in comparison to the natural history of the infection, the process was treated as a Markov simulation. The stages of the disease process were described as those who were susceptible to infection, those infected and those who removed themselves from the population (removals) or died. Their results demonstrate a high sensitivity to very small changes in the interaction levels within the groups and to changes to the probability of infection through a single contact with an infected person. The use of a closed population was seen as a limitation to this model and the authors speculated that an open population would allow them to assess how a reduction in the level of interaction would affect the prevalence rates.

Law (1999) developed models of the hepatitis C epidemic in Australia based on estimates of the pattern of injecting drug use. Due to the paucity of accurate data on the numbers of injecting drug users in Australia, the Delphi technique was used to achieve consensus estimates for the number of regular and occasional IDU's. Seventeen experts participated by completing a brief questionnaire used to estimate regular and occasional injecting drug use, with a second iteration performed by all participants. It was estimated that there were 100,000 regular and 175,000 occasional injecting drug users in Australia in 1997. Assumptions such as the HCV incidence rate among both groups, infection rates from transfusion or other transmission routes, the natural history of the disease and progression to cirrhosis and hepatocellular carcoinoma (HCC) were made from existing

studies or Government reports. Because of the uncertainty of some of these assumptions, extensive sensitivity analyses were performed on these parameters using upper and lower limits.

The models developed by Law indicated there were 196,000 (range 149,000 - 234,000) individuals with hepatitis C in Australia in 1997, increasing at a rate of 11,000 (range 8,500 – 13,500) new infections. The models also indicate 47,000 (35,000 - 60,000) had cleared the disease, 134,000 (101,000 – 167,000) had chronic HCV infection, 8,500 (4,000 – 13,000) has HCV-related cirrhosis and 80 (40 – 130) had develop HCC in 1997.

Kane et. al. (1999) produced a simple mass-action model utilising a general linear equation with variables representing the prevalence of a pathogen in a population, the transmission efficiency of the pathogen, the susceptibility of a population to that pathogen, the transmission efficiency of the pathogen, the proportion of unsafe injections and the number of injections a person receives. This research, prepared for the World Health Organisation, specifically addressed unsafe injecting practices among developing countries, where immunisation programs and medications are delivered via reused, unsterilised needles. The equation used to estimate an individuals risk of becoming infected is:

$$P(T) = 1 - (1 - P(s).P(t).P(e))^n$$

where *P(T)* is the probability of an individual becoming infected each year, *P(s)* is the probability that an individual is susceptible to the pathogen, *P(t)* is the probability that the organism will be transmitted via injecting equipment contaminated with infected blood, *P(e)* is the probability the individual is exposed to contaminated injecting

equipment and *n* is the number of injections an individual receives in one year. *P(e)* is a function of the prevalence of a virus, *P(v)* and the proportion of injections that are unsafe, *P(u)*, where *P(e)* = *P(v).P(u)*. Susceptibility was a function of HCV in the particular population, where *P(s)* = *1 - Prevalence(HCV-positive individuals)*. The simple mass-action linear model estimated 2.3 – 4.7 HCV infections per year resulting from unsafe injecting practices in the developing world. The authors go on to qualify their results, indicating there is no practical way to estimate the number of injections given outside the health sector in these countries, and that more complex, stratified models may produce more accurate estimates.

In a dissertation prepared by Zhanhai Gao (2001), mathematical models were prepared to model the human immunodeficiency viruse (HIV) and hepatitis C virus (HCV) epidemics in Australia. Gao derives a dynamical model of the HIV and HCV epidemics through needle sharing among injecting drug users and simulations of the prevalence and incidence of these viruses among IDU's are made. The effects of needle sharing and cleaning of equipment is examined. The second part of his model assesses the epidemiological consequences of injecting drug use and sexual transmission of HIV in Australia and examines the effect of highly active antiretroviral therapies on the HIV epidemic.

In 2003, Freeman and associates conducted an ecologic analysis to predict the progression of cirrhosis in chronic hepatitis C virus infection. The ecologic analysis was used to estimate the relative risk of cirrhosis for factors identified as significant in fibrosis progression. Factors included ethnicity, sex distribution, alcohol consumption,

age at infection, mode of HCV infection, serum transanimase levels, histological evidence of infection, HBV status, HIV co-infection and viral load. A time period of 20 years of HCV infection was used. In order for the relative risk of cirrhosis to be estimated using linear regression techniques, a transformation was performed: $y = \ln\{-\ln[1 - cirrhosis(20)]\}$ and then least squares linear regression lines were fitted for $y = \mu_{study\ category} + x\beta_{factor}$. Confidence intervals were based on the standard error of the slope of the regression line. The relative risk of cirrhosis, $RR_{factor} = \exp(\beta_{factor})$, was estimated and a stepwise multiple linear regression was performed to adjust for colinearity between factors.

Feeeman et. al. found that male sex (RR = 1.08), heavy alcohol consumption(RR = 1.61), elevated serum ALT (RR = 1.23) and histology demonstrating high-grade necroinflammatory activity were all factors independently associated with progression to cirrhosis. Other factors were not found to be significantly influential.

Law et. al. (2003), refined earlier published models, (Law, 1999), to provide a overview of HCV incidence, prevalence and long-term prognosis in 2001. Using methods described previously (Law, 1999), and recent published data from research and government reports, a more accurate picture of the incidence and prevalence of HCV infection in Australia was developed. Their results indicated that in 2001, the number of people with HCV antibodies numbered 210,000 (157,000 – 252,000) with and incidence rate of 16,000 (11,000 – 19,000) that year. Of these 83% of cases were estimated to be due to injecting drug use, 5% due to blood transfusions and 9% due to other transmission routes. They further estimated that by 2020, there would be 836,000 Australians living

with HCV infection. The number of individuals with cirrhosis, in 2001, was estimated to be 6,500 (5,000 – 8,000) and 50 (40 – 60) cases of HCC.

Murray et. al. (2003) constructed a mathematical model using differential equations to assess the impact of behavioural changes on the spread of HIV and HCV among injecting drug users. The model described *I(t)* the number of IDU's who are infectious at time *t*. Parameters for this model are; *al*, the average rate of new infections per year, *bl*, the average rate of loss each year of infected IDU's through all means and *c*, the rate of new infections per year from non-needle-sharing means. This gives:

$$\frac{dI}{dt} = aI - bI + c$$

The parameter, *a*, is calculated, $a = p(1-d)mu(n,\alpha)$, where *p* is the probability of infection through sharing a needle or equipment, *n* is the average number of IDU's using the same equipment per episode, *m* is the average number of injecting episodes per year, *d* is the fraction of needles that are cleaned before use, and *u* is the number of uninfected IDU's at risk.

For each individual, the number of people they have shared needles with over one year is defined by *m(n-1)*. The critical sharing level for incidence $s_{ci} \equiv m_{ci}(n_{ci}-1)/2$, is determined when

$$\begin{aligned} b &= a_{ci} \\ &= p(1-d)m_{ci}(n_{ci}-1)/2 \end{aligned}$$

Hence

$$s_{ci} = m_{ci}(n_{ci}-1) = \frac{2b}{p(1-d)}$$

Critical sharing levels for prevalence, s_{cp}, are calculated;

$s_{cp} = m_{cp}(n_{cp} - 1) = \frac{2(b+r)}{p(1-d)}$, where r is the annual rate of increase in total IDU numbers.

The authors discussed their results in light of the impact that needle exchange programs and the resulting lowering of needle sharing. The impact on the incidence of HIV after the late 1980's is quite marked however the impact on HCV incidence is less so. This is thought to be due to higher infectivity of HCV through needle sharing than HIV.

3.2 Mathematical Models.

It is proposed to initially construct a single sex model of the SIR form described by Anderson and May, 1989, utilising three separate stages, those Susceptible (S), those Infectious (I) and those in the Removal (R) category. The use of non-linear differential equation transmission models will be employed.

The population will be divided into three categories; those susceptible to infection (susceptibles), those currently infected (infectious) and those that progress to a chronic, non-infectious state or death (removals). Unlike models constructed to simulate HIV/AIDS transmission, where removals are designated by conversion to AIDS, hepatitis C does not have a clear transition stage. Development of cirrhosis or hepatocellular carcinoma will be used as the point of transition to the removals category.

The model will be age dependent with subgroups that denote duration of injecting. This subgroup structure arises from studies outlined in Chapter 2, where one of the key factors of HCV transmission related to duration of drug use. In Table 5 (Croft et. al., 1993), we see how prevalence rates are dependent on the number of years the individual has been injecting drugs. For this reason these subgroup will be divided in the same manner and will be denoted as 1, those with 0-4 years injecting; 2, those with 5-9 years injecting; 3, those with 10-14 years injecting and 4, those with 15 or more years injecting.

As explained by Anderson and May, 1989, the number of susceptible IVDU's increase due to recruitment and decrease following transition to the infectious class after needle sharing. A decrease in the infectious class occurs as a result of normal migration rates out of injecting populations. The rate of change in the number of infectious depends on recruitment from susceptibles and where transition to active hepatitis C and cirrhosis/hepatocellular carcinoma among infectious occurs. A natural attrition for both susceptibles and infectious will also occur due to death by drug and other disease-related causes. Finally the rate of change in the removals class is determined by those that are infectious and develop cirrhosis/hepatocellular carcinoma, and loss due to death and normal migration out of the drug using population.

Once developed the model will be solved by numerical approximation techniques, described more fully later in this chapter, and the Microsoft Excel spreadsheet. Computer simulations of the spread of hepatitis C through the IDU population will be performed. These will concentrate on providing estimates of the prevalence of hepatitis C in the drug using community of Perth, Western Australian as they move from one

subgroup to another (susceptible to infectious, infectious to removals) using varying IDU population denominators.

Once a comprehensive model has been developed it can then be refined to include accurate estimates of injecting drug users, who in 20 years time fall into the susceptible, infectious or removals categories. This information will then be used to estimate the cost of treating those persons with active HCV infection and those with cirrhosis or HCC.

3.2.1 Model 1

The initial model is designed to simulate a simple rate of needle sharing model, where gender differences and length of use are not considered. An important difference between the models described below and previous work done on HIV/AIDS transmission using SIR models is the interaction between susceptibles, infectious and removals. While development of cirrhosis is judged to be the transition point to the removals category, many individuals in this group remain asymptomatic for many years and will continue to inject drugs and interact with individuals in the other two groups.

This basic model is:

X(t) the number of injecting drug users susceptible to contracting hepatitis C,

Y(t) the number of injecting drug users infected with hepatitis C,

A(t) the number of injecting drug users with cirrhosis of the liver or hepatocellular carcinoma, and

P(t) the total population of injecting drug users

$$\frac{dX(t)}{dt} = \Lambda - n\hat{\beta}X(t)\frac{Y(t)+A(t)}{P(t)} - \mu X(t)$$

$$\frac{dY(t)}{dt} = n\hat{\beta}X(t)\frac{Y(t)+A(t)}{P(t)} - (\mu+\alpha)Y(t)$$

$$\frac{dA(t)}{dt} = \alpha Y(t) - (\mu+\delta)A(t)$$

$$P(t) = X(t) + Y(t) + A(t)$$

where

Λ = the recruitment rate to the IDU population

$\frac{1}{\alpha}$ = the mean incubation period for hepatitis C

δ = the cirrhosis/hepatocellular carcinoma related death rate

μ = the migration rate out of the population

$\hat{\beta}$ = the probability of transmission during a single needle sharing act

n = the rate of needle sharing per unit time

3.2.2 Model 2.

This second model incorporates the major transmission factor: - length of time engaged in injecting drug use. Four groups have been established where group 1 consists of those injecting for less than five years, group 2 those injecting for 5-9 years, group 3 those injecting for 10-15 years and group 4 those injecting for greater than 15 years. Groups are identified by the subscripts 1 to 4, where $X_1(t)$ represents the number of susceptible individuals in group 1 at time t.

This model also has those in the removals category continuing to mix with those who are susceptible or infectious. The groupings reflect length of time an individual has been engaged in injecting drugs and given the nature of their interactions with other IDU's, they are equally likely to be mixing with individuals of other groups. A person who has been injecting drugs for three years has an equally likely chance of interacting with others who have been injecting for eight, ten or fifteen years, especially if their lifestyle has marginalised them from society. As such the model reflects this likelihood of an individual, i.e. $X_1(t)$ having the opportunity of sharing injecting equipment from all other infectious and removals.

The model, when simulated, has monthly iterations. Thus for a twenty year projection, 240 iterations are performed. To reflect this monthly simulation, the movement through the susceptible, infectious, and removals categories are also incremented monthly, reflect by the proportion, $\frac{1}{60}$.

This model now becomes:

$$\frac{dX_1(t)}{dt} = \Lambda - n\hat{\beta}X_1(t)\frac{Y(t)+A(t)}{P(t)} - \mu X_1(t) - \frac{1}{60}X_1(t)$$

$$\frac{dX_2(t)}{dt} = -n\hat{\beta}X_2(t)\frac{Y(t)+A(t)}{P(t)} - \mu X_2(t) + \frac{1}{60}(X_1(t) - X_2(t))$$

$$\frac{dX_3(t)}{dt} = -n\hat{\beta}X_3(t)\frac{Y(t)+A(t)}{P(t)} - \mu X_3(t) + \frac{1}{60}(X_2(t) - X_3(t))$$

$$\frac{dX_4(t)}{dt} = -n\hat{\beta}X_4(t)\frac{Y(t)+A(t)}{P(t)} - \mu X_4(t) + \frac{1}{60}X_3(t)$$

$$\frac{dY_1(t)}{dt} = n\hat{\beta}X_1(t)\frac{Y(t)+A(t)}{P(t)} - (\mu+\alpha)Y_1(t) - \frac{1}{60}Y_1(t)$$

$$\frac{dY_2(t)}{dt} = n\hat{\beta}X_2(t)\frac{Y(t)+A(t)}{P(t)} - (\mu+\alpha)Y_2(t) + \frac{1}{60}(Y_1(t) - Y_2(t))$$

$$\frac{dY_3(t)}{dt} = n\hat{\beta}X_3(t)\frac{Y(t)+A(t)}{P(t)} - (\mu+\alpha)Y_3(t) + \frac{1}{60}(Y_2(t) - Y_3(t))$$

$$\frac{dY_4(t)}{dt} = n\hat{\beta}X_4(t)\frac{Y(t)+A(t)}{P(t)} - (\mu+\alpha)Y_4(t) + \frac{1}{60}Y_3(t)$$

$$\frac{dA_1(t)}{dt} = \alpha Y_1(t) - (\mu+\delta)A_1(t) - \frac{1}{60}A_1(t)$$

$$\frac{dA_2(t)}{dt} = \alpha Y_2(t) - (\mu+\delta)A_2(t) + \frac{1}{60}(A_1(t) - A_2(t))$$

$$\frac{dA_3(t)}{dt} = \alpha Y_3(t) - (\mu+\delta)A_3(t) + \frac{1}{60}(A_2(t) - A_3(t))$$

$$\frac{dA_4(t)}{dt} = \alpha Y_4(t) - (\mu+\delta)A_4(t) + \frac{1}{60}A_3(t)$$

$$P(t) = \sum_{i=1}^{4}(X_i(t) + Y_i(t) + A_i(t))$$

where

Λ = the recruitment rate to the IDU population

$\frac{1}{\alpha}$ = the mean incubation period for hepatitis C

δ = the cirrhosis/hepatocellular carcinoma related death rate

μ = the migration rate out of the population

$\hat{\beta}$ = the probability of transmission during a single needle sharing act

n = the rate of needle sharing per unit time

3.3 Numerical Approximation Techniques:

3.2.1 Euler's Method.

Euler's Method (Gerald and Wheatley) is a numerical technique that employs the first two terms of the Taylor-series

$$y(x) = y(x_0) + y'(x_0)(x - x_0) + \frac{y''(x_0)}{2!}(x - x_0)^2 + \frac{y'''(x_0)}{3!}(x - x_0)^3 + \ldots\ldots$$

to approximate the solution to first order differential equations. This method relies on the step size h being small enough to allow truncation of the Taylor-series after the first derivative term. This gives

$$y(x_0 + h) = y(x_0) + h\,y'(x_0) + \frac{y''(\xi)h^2}{2} \qquad x_0 < \xi < x_0 + h$$

(ξ error term)

Here $y(x_0)$ is given by the initial condition and $y'(x_0)$ is evaluated from $f(x_0,y_0)$ given by the differential equation, $dy/dx = f(x,y)$. This method is an iterative method, advancing the solution, $y(x_0 + h)$, $y(x_1 + h)$, $y(x_2 + h)$ etc.

The algorithm for Euler's Method may be expressed:

$$y_{n+1} = y_n + hy'_n + O(h^2) \qquad (O(h^2) \text{ the local error})$$

A major limitation of Euler's method in approximating first order differential equations is, unless the step is extremely small it lacks accuracy (see Figure 4).

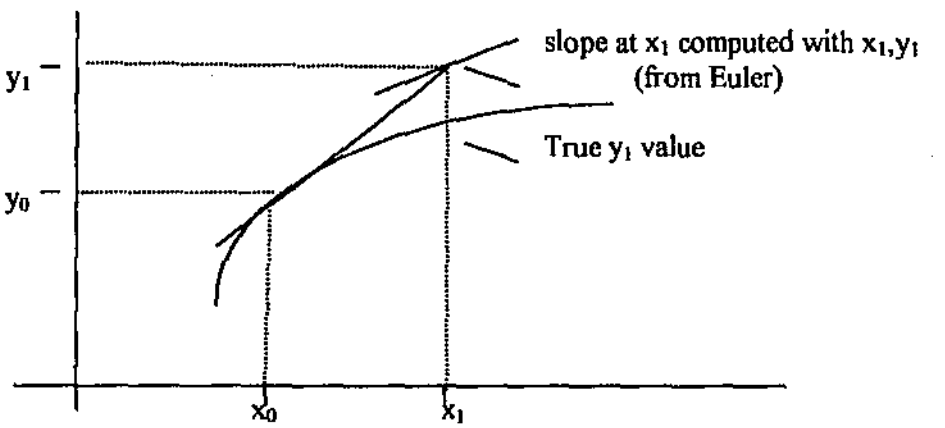

Figure 4. Lack of accuracy of Euler's Method.

3.3.2 Modified Euler's Method.

In order to calculate the correct average slope between y_n and y_{n+1} it is necessary to calculate the mean of the slopes at both ends of the interval. This could be done by using

$$y_{n+1} = y_n + h\frac{y'_n + y'_{n+1}}{2}$$

Unfortunately it is not possible to evaluate y'_{n+1} when y_{n+1} is unknown. The modified Euler method overcomes this by estimating a value of y_{n+1} using Eulers method (3.3.1) and then using this value to compute y'_{n+1} giving an improved value for y_{n+1}.

3.4. Computational Methods.

3.4.1 Model 1 Using Eulers Method.

The model was approximated with Euler's Method using Excel v5.0 for Windows.

Parameters used were:

Lambda	the recruitment rate to the IDU population (per month)
n	the rate of needle sharing per unit time (per month)
betahat	the probability of transmission per act of needle sharing
x(0)	the number of IDU susceptibles at the start of the simulation
y(0)	the number of IDU infectious at the start of the simulation
mu	migration rate out of the population (per month)
alpha	1/alpha = mean incubation period (in months)
delta	death rate due to HCC/cirrhosis (per month)
a(0)	number of IDU cirrhosis/HCC cases at start of simulation
hx	step for x
hy	step for y
ha	step for a.

hx, hy and ha all represent the step increment of the Eulers model. To distinguish between the theoretical model and the computational model, now $x(0) = X(0)$, the initial number of susceptibles at time, $t = 0$.

The computations for the model involved the following steps:

x Iteration 1: $= x(0)$

Iteration j≥2: $= x_{j-1} + (x'_{j-1} * hx)$

y Iteration 1: $= y(0)$

Iteration j≥2: $= y_{j-1} + (y'_{j-1} * hy)$

a Iteration 1: $= a(0)$

Iteration j≥2: $= a_{j-1} + (a_{j-1} * ha)$

p Iteration 1: $= x_j + y_j + a_j$

x'_j $=lambda-(n*betahat*x_j*((y_j+a_j)/p_j))-(mu*x_j)$

y'_j $=(n*betahat*x_j*((y_j+a_j)/p_j)-((mu+alpha)*y_j)$

a'_j $=(alpha*y_j)-((mu+delta)*a_j)$

3.4.2 Model 1 and Modified Euler's Method.

The model was approximated with the modified Euler's method using Excel v5.0 for Windows. Parameters used were:

Lambda	the recruitment rate to the IDU population (per month)
n	the rate of needle sharing per unit time (per month)
betahat	the probability of transmission per act of needle sharing
x(0)	the number of IDU susceptibles at the start of the simulation

y(0)	the number of IDU infectious at the start of the simulation
mu	migration rate out of the population (per month)
alpha	1/alpha = mean incubation period (in months)
delta	death rate due to HCC/cirrhosis (per month)
a(0)	number of IDU cirrhosis/HCC cases at start of simulation
hx	step for x
hy	step for y
ha	step for a.

hx, hy and ha all represent the step increment of the Euler's model.

The computations for the model involved the following steps:

x	Iteration 1:	$= x(0)$
	Iteration j≥2:	$= x_{j-1} + (hx*((k1+k2)/2)$
newx	Iteration j:	$newx_j = x_j + (hx*k1)$
y	Iteration 1:	$= y(0)$
	Iteration j≥2:	$= y_{j-1} + (hy*((k3+k4)/2))$
newy	Iteration j:	$newy_j = y_j + (hy*k3)$
a	Iteration 1:	$= a(0)$
	Iteration j≥2:	$= a_{j-1} + (ha*((k5+k6)/2))$
newa	Iteration j:	$newa_j = a_j + (ha*k5)$
p	Iteration j	$= x_j + y_j + a_j$

newp		Iteration j	$newp_j = newx_j + newy_j + newa_j$
x'_j	k1:	Iteration j	$=lambda-(n*betahat*x_j*((y_j+a_j)/p_j))-(mu*x_j)$
	k2:	Iteration j	$= lambda-(n*betahat*newx_j*((newy_j+newa_j)/newp_j)-(mu*newx_j)$
y'_j	k3	Iteration j	$=(n*betahat*x_j*((y_j+a_j)/p_j))-((mu+alpha)*y_j)$
	k4	Iteration j	$=(n*betahat*newx_j*((newy_j+newa_j)/newp_j))-((mu+alpha)*newy_j)$
a'_j	k5	Iteration j	$=(alpha*y_j)-((mu+delta)*a_j)$
	k6	Iteration j	$=(alpha*newy_j)-((mu+delta)*newa_j)$

3.4.3 Model 2 and Euler's Method.

This was the first simulation of hepatitis C transmission using length of injecting drug use. As we saw in Chapter 2, persons infected with hepatitis C are not diagnosed with cirrhosis of the liver or hepatocellular carcinoma less than 15 years after commencing injecting. For this reason, only one group is used for those in the removals category, namely a4. The model was approximated with Euler's method using Excel v5.0 for Windows. Parameters used were:

Lambda	the recruitment rate to the IDU population (per month)
n	the rate of needle sharing per unit time (per month)

betahat	the probability of transmission per act of needle sharing
x1(0)	number of IDU susceptibles at start of simulation using 0-4 yrs
x2(0)	number of IDU susceptibles at start of simulation using 5-9 yrs
x3(0)	number of IDU susceptibles at start of simulation using 10-14 ys
x4(0)	number of IDU susceptibles at start of simulation using 15+ yrs
y1(0)	number of IDU infectious at start of simulation using 0-4 yrs
y2(0)	number of IDU infectious at start of simulation using 5-9 yrs
y3(0)	number of IDU infectious at start of simulation using 10-14 yrs
y4(0)	number of IDU infectious at start of simulation using 15+ yrs
p(0)	Total number of IVDU's at start of simulation
mu	migration rate out of the population (per month)
alpha	1/alpha = mean incubation period (in months)
delta	death rate due to HCC/cirrhosis (per month)
a4(0)	number of IDU cirrhosis/HCC cases at start of simulation using 15+ years
hx	step for x
hy	step for y
ha	step for a.

hx, hy and ha all represent the step increment of the Euler's model.

The computations for the model involved the following steps:

x1	Iteration 1:	$= x1(0)$
	Iteration j≥2:	$= x1_{j-1} + (x1'_{j-1} * hx)$
x2	Iteration 1:	$= x2(0)$

	Iteration j≥2:	$= x2_{j-1} + (x2'_{j-1} * hx)$
x3	Iteration 1:	$= x3(0)$
	Iteration j≥2:	$= x3_{j-1} + (x3'_{j-1} * hx)$
x4	Iteration 1:	$= x4(0)$
	Iteration j≥2:	$= x4_{j-1} + (x4'_{j-1} * hx)$
x	Iteration 1:	$x_1 = x1(0) + x2(0) + x3(0) + x4(0)$
	Iteration j≥2:	$x_j = x1_j + x2_j + x3_j + x4_j$
y1	Iteration 1:	$= y1(0)$
	Iteration j≥2:	$= y1_{j-1} + (y1'_{j-1} * hy)$
y2	Iteration 1:	$= y2(0)$
	Iteration j≥2:	$= y2_{j-1} + (y2'_{j-1} * hy)$
y3	Iteration 1:	$= y3(0)$
	Iteration j≥2:	$= y3_{j-1} + (y3'_{j-1} * hy)$
y4	Iteration 1:	$= y4(0)$
	Iteration j≥2:	$= y4_{j-1} + (y4'_{j-1} * hy)$
y	Iteration 1:	$y_1 = y1(0) + y2(0) + y3(0) + y4(0)$
	Iteration j≥2:	$y_j = y1_j + y2_j + y3_j + y4_j$
a4	Iteration 1:	$= a4(0)$
	Iteration j≥2:	$= a4_{j-1} + (a4'_{j-1} * ha)$
p_j	Iteration j	$p_j = x_j + y_j + a_j$

$x1'$ Iteration j $= lambda-(n*betahat*x1_j*((y_j + a_j)/p_j))-(mu*x1_j)-1/60*x1_j$

$x2'$ Iteration j $= -(n*betahat*x2_j*((y_j + a_j)/p_j))-(mu*x2_j) + (1/60*(x1_j-x2_j))$

$x3'$ Iteration j $= -(n*betahat*x3_j*((y_j + a_j)/p_j))-(mu*x3_j) + (1/60*(x2_j-x3_j))$

$x4'$ Iteration j $= -(n*betahat*x4_j*((y_j + a_j)/p_j))-(mu*x4_j) + (1/60*x3_j)$

$y1'$ Iteration j $= (n*betahat*x1_j*((y_j + a_j)/p_j))-((mu + alpha)*y1_j) - 1/60*y1_j$

$y2'$ Iteration j $= (n*betahat*x2_j*((y_j + a_j)/p_j))-((mu + alpha)*y2_j) + (1/60*(y1_j - y2_j))$

$y3'$ Iteration j $= (n*betahat*x3_j*((y_j + a_j)/p_j))-((mu + alpha)*y3_j) + (1/60*(y2_j-y3_j))$

$y4'$ Iteration j $(n*betahat*x4_j*((y_j + a_j)/p_j))-((mu + alpha)*y4_j) + (1/60*y3_j)$

$a4'$ Iteration j $= (alpha*y4_j)-((mu + delta)*a4_j)$

3.4.4 Model 2 and Modified Euler's Method.

Once again because persons infected with hepatitis C are not diagnosed with cirrhosis of the liver or hepatocellular carcinoma less than 15 years after commencing injecting only one group is used for those in the removals category, namely a4. The model was approximated with modified Euler's Method using Excel v5.0 for Windows. Parameters used were:

Lambda	the recruitment rate to the IDU population (per month)
n	the rate of needle sharing per unit time (per month)
betahat	the probability of transmission per act of needle sharing

x1(0)	number of IDU susceptibles at start of simulation using 0-4 yrs
x2(0)	number of IDU susceptibles at start of simulation using 5-9 yrs
x3(0)	number of IDU susceptibles at start of simulation using 10-14 ys
x4(0)	number of IDU susceptibles at start of simulation using 15+ yrs
y1(0)	number of IDU infectious at start of simulation using 0-4 yrs
y2(0)	number of IDU infectious at start of simulation using 5-9 yrs
y3(0)	number of IDU infectious at start of simulation using 10-14 yrs
y4(0)	number of IDU infectious at start of simulation using 15+ yrs
p(0)	Total number of IVDU's at start of simulation
mu	migration rate out of the population (per month)
alpha	1/alpha = mean incubation period (in months)
delta	death rate due to HCC/Cirrhosis (per month)
a4(0)	number of IDU Cirrhosis/HCC cases at start of simulation using 15+ years
hx	step for x
hy	step for y
ha	step for a.

hx, hy and ha all represent the step increment of the Euler's model.

The computations for the model involved the following steps:

x1	Iteration 1:	$= x1(0)$
	Iteration j≥2:	$= x1_{j-1} + (hx*((k11_j + k21_j)/2)$
newx1	Iteration j:	$newx1_j = x1_j + (hx*k11_j)$

x2	Iteration 1:	$= x2(0)$
	Iteration j≥2:	$= x2_{j-1} + (hx*((k12_j + k22_j)/2)$
newx2	Iteration j:	$newx2_j = x2_j + (hx*k12_j)$
x3	Iteration 1:	$= x3(0)$
	Iteration j≥2:	$= x3_{j-1} + (hx*((k13_j + k23_j)/2)$
newx3	Iteration j:	$newx3_j = x3_j + (hx*k13_j)$
x4	Iteration 1:	$= x4(0)$
	Iteration j≥2:	$= x4_{j-1} + (hx*((k14_j + k24_j)/2)$
newx4	Iteration j:	$newx4_j = x4_j + (hx*k14_j)$

$x_1 = x1(0) + x2(0) + x3(0) + x4(0)$

$x_j = x1_j + x2_j + x3_j + x4_j$

$newx_j = newx1_j + newx2_j + newx3_j + newx4_j$

y1	Iteration 1:	$= y1(0)$
	Iteration j≥2:	$= y1_{j-1} + (hy*((k31_j + k41_j)/2)$
newy1	Iteration j:	$newy1_j = y1_j + (hy*k31_j)$
y2	Iteration 1:	$= y2(0)$
	Iteration j≥2:	$= y2_{j-1} + (hy*((k32_j + k42_j)/2)$
newy2	Iteration j:	$newy2_j = y2_j + (hy*k32_j)$
y3	Iteration 1:	$= y3(0)$
	Iteration j≥2:	$= y3_{j-1} + (hy*((k33_j + k43_j)/2)$

newy3		Iteration j:	$newy3_j = y3_j + (hy*k33_j)$

y4		Iteration 1:	$= y4(0)$
		Iteration j≥2:	$= y4_{j-1} + (hy*((k34_j + k44_j)/2)$
newy4		Iteration j:	$newy4_j = y4_j + (hy*k34_j)$

$y_1 = y1(0) + y2(0) + y3(0) + y4(0)$

$y_j = y1_j + y2_j + y3_j + y4_j$

$newy_j = newy1_j + newy2_j + newy3_j + newy4_j$

a4		Iteration 1:	= a4(0)
		Iteration j≥2:	$= a4_{j-1} + (ha*((k54_j + k64_j)/2)$
newa4		Iteration j:	$newa4_j = a4_j + (ha*k54_j)$

$newz_j = newy_j + newa4_j$

p_j		Iteration j	$p_j = x_j + y_j + a_j$
newp		Iteration j	$newp_j = newx_j + newy_j + newa_j$

$x1'$	k11	Iteration j	$= lambda-(n*betahat*x1_j*((y_j + a_j)/p_j))-(mu*x1_j)$
	k21	Iteration j	$= lambda-(n*betahat*newx1_j*(newz_j/newp_j)) -$ $(mu*newx1_j) - (1.60*newx1_j)$

$x2'$	k12	Iteration j	$= -(n*betahat*x2_j*((y_j + a_j)/p_j))-(mu*x2_j) + (1/60*(x1_j - x2_j))$
	k22	Iteration j	$= -(n*betahat*(newx2_j)*(newz_j/newp_j)) - (mu*newx2_j) + (1/60*(newx1_j - newx2_j))$
$x3'$	k13	Iteration j	$= -(n*betahat*x3_j*((y_j + a_j)/p_j))-(mu*x3_j) + (1/60*(x2_j - x3_j))$
	k23	Iteration j	$= -(n*betahat*newx3_j)*(newz_j/newp_j))- (mu*newx3_j) + (1/60*(newx2_j - newx3_j)$
$x4'$	k14	Iteration j	$= -(n*betahat*x4_j*((y_j + a_j)/p_j))-(mu*x4_j) + (1/60*x3_j)$
	k24	Iteration j	$= -(n*betahat*newx4_j)*(newz_j/newp_j))- (mu*newx4_j) + (1/60*newx3_j)$
$y1'$	k31	Iteration j	$= (n*betahat*x1_j*((y_j + a_j)/p_j))-((mu + alpha)*y1_j) - (1/60*y1_j)$
	k41	Iteration j	$= (n*betahat*newx1_j*(newz_j/newp_j))- ((mu + alpha)*(newy1_j)) - (1/60*newy1_j)$
$y2'$	k32	Iteration j	$= (n*betahat*x2_j*((y_j + a_j)/p_j))-((mu + alpha)*y2_j) + (1/60 *(y1_j - y2_j)$
	k42	Iteration j	$= (n*betahat*newx2_j*(newz_j/newp_j))-((mu + alpha) *(newy2_j)) + (1/60*(newy1_j - newy2_j)$
$y3'$	k33	Iteration j	$= (n*betahat*x3_j*((y_j + a_j)/p_j))-((mu + alpha)*y3_j) + (1/60 *(y2_j - y3_j)$
	k43	Iteration j	$= (n*betahat*newx3_j*(newz_j/newp_j))- ((mu + alpha)*(newy3_j)) + (1/60*(newy2_j - newy3_j))$

$y4'$	k34	Iteration j	$= (n*betahat*x4_j*((y_j + a_j)/p_j)) - ((mu + alpha)*y4_j) + (1/60*y3_j)$
	k44	Iteration j	$= (n*betahat*newx4_j*(newz_j/newp_j)) - ((mu + alpha)*(newy4_j)) + (1/60*newy3_j)$
$a4'$	k54	Iteration j	$= (alpha*y4_j) - ((mu + delta)*a4_j)$
	k64	Iteration j	$= (alpha*newy4_j) - ((mu + delta)*newa4_j)$

To summarise, two models were developed using two approximation techniques. The Euler 1 model produces results equivalent to those produced by Euler 2 (the model incorporating length of drug use). The modified Euler's model 1 also produces result equivalent to the modified Euler's 2 model (the model incorporating length of drug use). This is expected as the same parameters were used to test all four models. There is a slight difference in results between the Euler models and the modified Euler's models, this being due to rounding. All further work was carried out using the modified Euler's method incorporating length of injecting drug use.

MODEL PARAMETERS

4.1 Population Sizes.

The model requires estimations of the number of persons in each risk group. These estimations will be based to a large extent on the population numbers of Western Australia. In 2001 (the last census year), the distribution of the Western Australian population, in five year age groups was as defined by Figure 5.

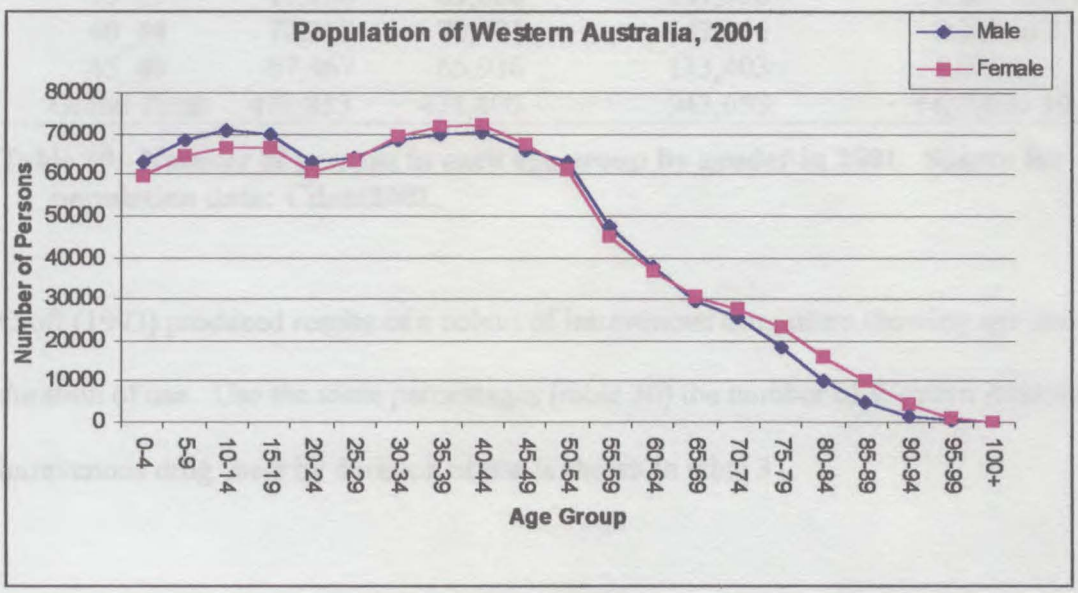

Figure 5. Population of Western Australia in 2001 by age group and gender. Source: Cdata2001

The population groups to be incorporated into the model are those aged 15 to 49 years, as seen in Chapter 2, these age groups represent those most at risk of HCV through injecting drug use. In 2001, 51.5% of the Western Australian population or 943, 653 persons were in this category (see table 30). Proportionately, Western Australia has 9.8% of the national population.

Given an estimated 150,000 to 200,000 intravenous drug users in Australia (Hulse, 1993; Wodak, 1994; Wodak, 1995; Wodak, 1997; Crofts, 2001), the number of IVDUs in Western Australia can be approximated to 14,700 to 19,600 persons.

Age group	Female	Male	Total population	Estimated number of IVDUs in WA
15_19	66,413	69,866	136,279	2,123 to 2,831
20_24	60,736	63,257	123,993	1,932 to 2,575
25_29	63,711	64,084	127,795	1,991 to 2,654
30_34	69,413	68,360	137,773	2,146 to 2,862
35_39	71,750	69,806	141,556	2,205 to 2,940
40_44	72,363	70,491	142,854	2,225 to 2,967
45_49	67,467	65,936	133,403	2,078 to 2,771
Grand Total	471,853	471,800	943,653	14,700 to 19,600

Table 30. Number of persons in each age group by gender in 2001. Source for population data: Cdata2001.

Croft (1993) produced results of a cohort of intravenous drug users showing age and duration of use. Use the same percentages (table 30) the number of Western Australian intravenous drug users by duration of use is shown in table 31.

	pop=14,700	pop=19,600
0-4 years	3,844	5,125
5-9 years	3,196	4,260
10-14 years	2,800	3,734
15+ years	4,860	6,480
total	14,700	19,600

Table 31. Estimated number of intravenous drug users in Western Australia by duration of use.

4.2 Number of IVDU cirrhosis/HCC Cases.

Literature suggests that approximately 20% of all cases of HCV (Crofts, 2001; Dore et. al. 2002; Freeman et. al. 2003; Law et. al. 2003.), develop cirrhosis over a 20 year period. This means that only those injecting for more than 15 years are eligible for inclusion in this category. The estimated number of IVDUs with cirrhosis or HCC are given below.

	cirrhosis (pop = 14700)	**cirrhosis (pop = 19600)**
0-4	0	0
5-9	0	0
10-14	0	0
15+	972	1296

Table 32. Estimated number of intravenous drug users with cirrhosis/HCC by duration of use in 2001.

4.3 Number of IVDU's with hepatitis C virus Infection.

Hepatitis C is a notifiable disease. The 1999 HIV/AIDS, Hepatitis C& Sexually Transmissible Infections in Australia: Annual Surveillance Report shows Western Australia had 4,502 new cases of hepatitis C infection in 1998 at a rate of 98.7 per 100,000. Literature suggests the incidence of hepatitis C among injecting drug users to be between 7% and 15% per year, (Mather and Crofts, 1999; Law, 1999; Crofts, 2001; Law et. al. 2003, Murray, et. al. 2003). As intravenous drug use is now acknowledged to be responsible for 75 to 85% of all new hepatitis C infections in Australia, this translates to between 3376 and 3827 new case of hepatitis C infection in Western Australia for 1998 due to intravenous drug use.

According to the 1999 HIV/AIDS, Hepatitis C & Sexually Transmissible Infections in Australia: Annual Surveillance Report, 17% of IVDU's injecting for less than 3 years were infected with the HCV virus nationally. Among those injecting for 3-5 years, 29% were infected and 69% infected among those injecting for 6 years or more. These figures are lower than those published by Crofts (1993) where he shows an infection rate of 38.6% for those injecting 0-4 years, a 70.9% infection rate for those injecting for 5-9 years, a 90% infection rate for those injecting for 10-14 years and 90.5% infected when injecting for 15 years or more. The 1999 HIV/AIDS, Hepatitis C & Sexually Transmissible Infections in Australia does not use the same age categories as those used by Crofts, however estimations will be made using these lower infection percentages to form a lower boundary, while the results of Crofts will be used as an upper boundary. Adjusting for the number of estimated cases with cirrhosis/HCC, we get:

Total	**infected (pop = 14,700)**		**infected (pop =19,600)**	
	Lower	Upper	Lower	Upper
0-4	654	1,484	871	1,978
5-9	2,205	2,266	2,940	3,021
10-14	1,932	2,520	2,576	3,360
15+	2,381	3,450	3,175	4,601
Total	7,121	9,668	9,563	12,961

Table 33. Estimated number of intravenous drug users infected with the hepatitis C virus by duration of use in 2001.

4.4 Number of IVDU's that do not have the hepatitis C virus.

After subtracting those who are infectious or have cirrhosis/HCC from the IVDU population we get:

Total	not infected (pop = 14,700)		not infected (pop =19,600)	
	Lower	Upper	Lower	Upper
0-4	3,191	2,360	4,254	3,147
5-9	991	930	1,321	1,240
10-14	868	280	1,157	373
15+	1,507	437	2,009	583
Total	6,533	3,986	8,741	5,343

Table 34. Estimated number of intravenous drug users not infected with the hepatitis C virus by duration of use in 2001.

4.5 Recruitment and Migration Rates.

No published material was available on the recruitment rate to the IVDU population. Murray (2003) estimates the rate of increase among IDU's in Australia was 7% until 1997 and 5% thereafter. Varying rates will be used with 7% as an upper bound for the model, given that the rates used by Murray are estimates.

If recruitment rates of 1%, 3%, 5% and 7% of the existing IVDU population are considered we get:

	1%	3%	5%	7%
pop = 14,700	147	441	735	1,029
pop = 19,600	196	588	980	1,372

Table 35. Estimated number of persons recruited to the IVDU per annum.

As the model currently estimates a monthly change all the above will be divided by 12. For the lack of any published material, it will be assumed that the migration rate out of the IVDU population will match the recruitment rate (for example, at a rate of 3%, the migration rate will equal 0.03/12 per month).

4.6 Rate of Needle Sharing per Unit Time

The 1999 HIV/AIDS, Hepatitis C & Sexually Transmissible Infections in Australia: Annual Surveillance Report indicates that 15% of IVDU's injecting in the past month and using for less than three years, shared needles and syringes. Likewise 14% of those using for three years or more and injecting in the last month shared needles and syringes. Thus if 15% of users share needles and syringes we have a rate of 0.15.

Total	% sharing needles and syringes	Rate of needle sharing per month.
0-4	15	0.15
5-9	14	0.14
10-14	14	0.14
15+	14	0.14

Table 36: Rate of needle sharing per month.

4.7 Probability of Transmission During a Single Needle Sharing Act.

Crofts, Aitken and Kaldor (1999) estimated the probability of infection with HCV from a needle sharing act was 1.3 to 4.9 (divided by 100). This estimate is consistent with an editorial by Watson (2000) where the risk of transmission by an individual needle stick is up to 6.1%.

4.8 Death Rate Due to hepatocellular carcinoma/cirrhosis.

The number of people at risk of dying from hepatocellular carcinoma or cirrhosis are drawn from the population injecting for fifteen years or more. Literature suggests that 10

years after a diagnosis of Cirrhosis, 75% were experiencing severe symptoms (Yano M et. al., 1996).

By calculating the proportion of persons with severe symptoms after 10 years and dividing by 12 to obtain a rate per month, the death rate due to hepatocellular carcinoma or cirrhosis is 0.00625.

SIMULATION RESULTS

5.1 Total Intravenous Drug Using population, 14,700

Parameters that will remain constant are 1) the mean incubation rate of six weeks results in a value of 0.6 [$\frac{1}{\alpha} = \frac{1}{1.5}$] and, 2) the rate in which hepatitis C progresses to cirrhosis. Evidence suggests a time span of 20 to 30 years, therefore the average of 25 years will be used resulting in a value of 0.003 [$\delta = \frac{1}{300}(25 * 12\,\text{months})$].

The probability of infection from a single needle sharing act is made up of two parameters, the rate of needle sharing per unit time (0.14) × probability of infection during a single needle sharing act. Crofts, Aitken and Kaldor estimated this to be 1.3 to 4.9, giving a low probability of infection from a single needle sharing act of 0.182 and a high probability of 0.686.

5.1.1 Population 14,700 with low infectivity rates and a low probability of infection from a single needle sharing act.

Using the rates of infection supplied by the 1999 HIV/AIDS, Hepatitis C & Sexually Transmissible Infections in Australia: Annual Surveillance report population numbers are as follows:

	0-4 years	5-9 years	10-14 years	15+ years
IVDU's that do not have HCV, X(t)	3,191	991	868	1,507
IVDU's who do have HCV, Y(t)	654	2,154	1,932	2,381
IVDU's with cirrhosis/HCC, A(t)	0	0	0	972
Rate of needle sharing per month, (n)	0.15	0.14	0.14	0.14
Parameters				
1% recruitment rate, (Λ)				147
Probability of transmission during single needle sharing act (β) (Rate of needle sharing*probability of infection)				0.182
Migration rate out of IVDU population, (μ)				1%
Mean incubation rate – 6 weeks, ($\frac{1}{\alpha}$)				$0.\overline{6}$
Death rate due to HCC/cirrhosis				0.00625
Rate at which hepatitis C develops into cirrhosis				$0.00\overline{3}$

Table 37. Parameters: Population 14,700, low infectivity rates and a low probability of infection from a single needle sharing act.

Using model 2 developed in Chapter 3 and the parameters described in Table 37, with initial conditions also in Table 37, we can provide the following output from the simulations.

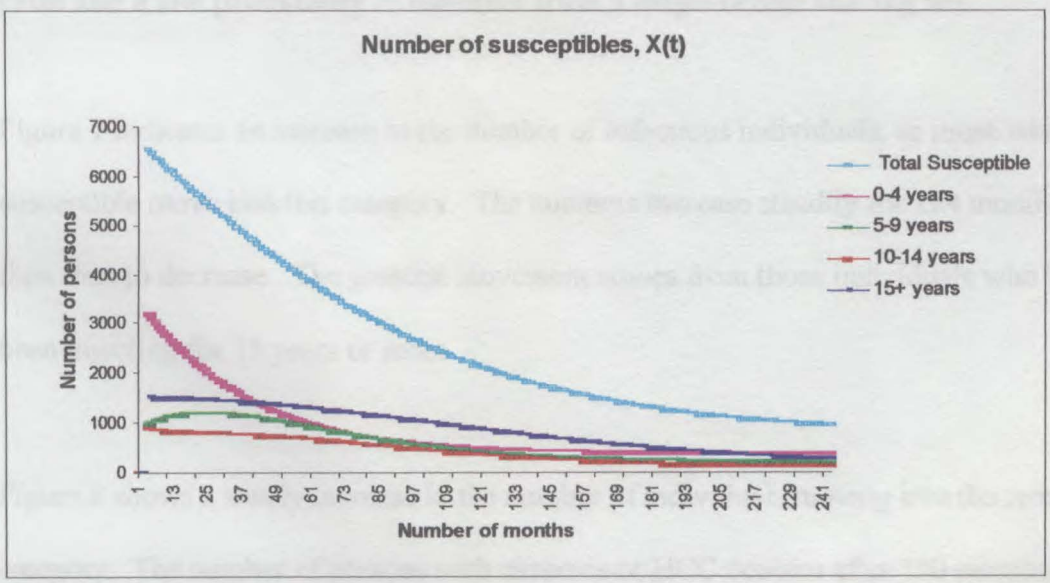

Figure 6. Number of susceptibles after 20 years, population 14,700, low infectivity rates and a low probability of infection from a single needle sharing act.

Figure 6 clearly illustrates a decline in the total susceptible population, with those in the 0 - 4 years injecting group in most rapid decline and those in the 10-14 years injecting group is the slowest. The population of susceptible IDU's is reduced by 50% after 74 months.

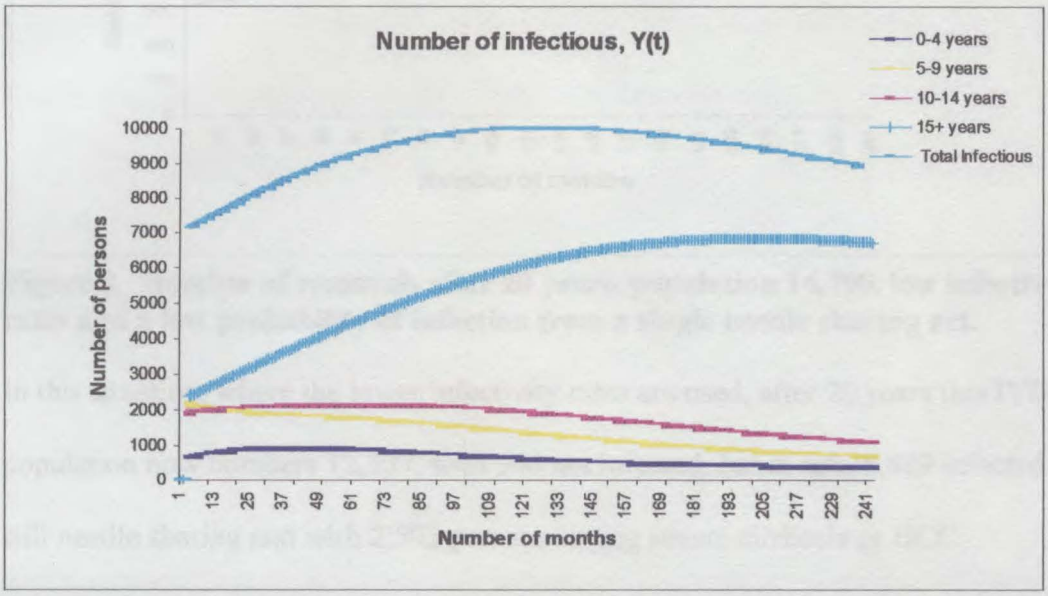

Figure 7. Number of infectious after 20 years, population 14,700, low infectivity rates and a low probability of infection from a single needle sharing act.

Figure 7 indicates an increase in the number of infectious individuals, as those who are susceptible move into this category. The numbers increase steadily for 124 months and then start to decrease. The greatest movement comes from those individuals who have been injecting for 15 years or more.

Figure 8 shows a steady increase in the number of individuals moving into the removals category. The number of persons with cirrhosis or HCC doubles after 160 months.

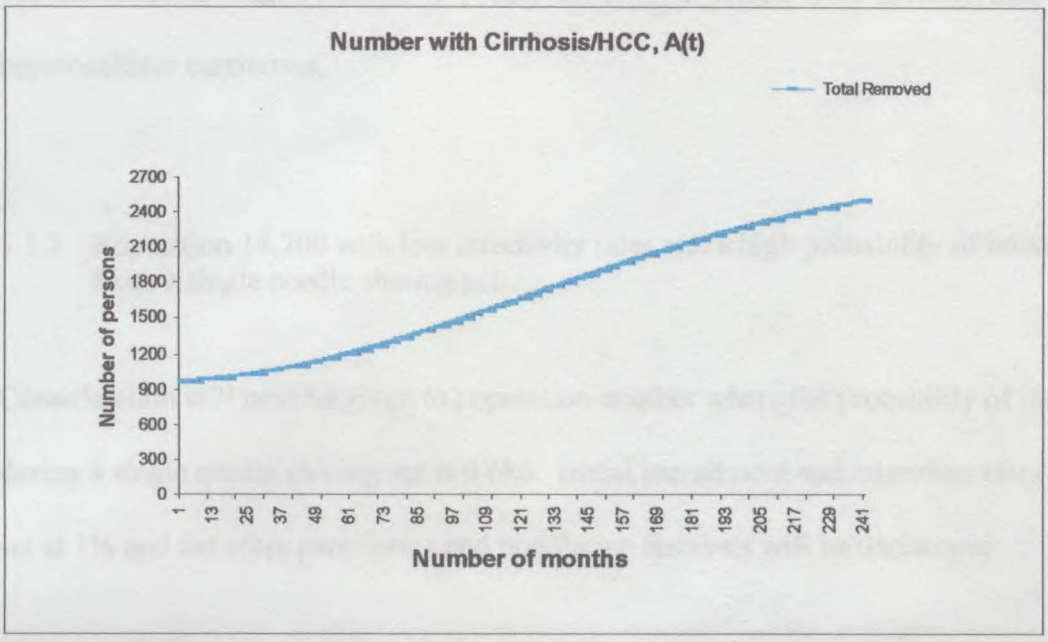

Figure 8. Number of removals after 20 years, population 14,700, low infectivity rates and a low probability of infection from a single needle sharing act.

In this situation, where the lower infectivity rates are used, after 20 years this IVDU population now numbers 12,337, with 946 not infected, but at risk, 8,889 infected and still needle sharing and with 2,502 persons having severe cirrhosis or HCC.

Using the same initial population numbers and probability of infection, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	2,426	8,838	1,814	13,078
5%	5%	3,884	8,383	1,318	13,585
7%	7%	5,299	7,677	958	13,935

Table 38. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

As the recruitment rate increases among this cohort the number of susceptible IVDU's increases. The corresponding migration rate show a movement out of the drug using

population and a smaller number of people suffering ill effects from cirrhosis and hepatocellular carcinoma.

5.1.2 Population 14,700 with low infectivity rates and a high probability of infection from a single needle sharing act.

Consideration will now be given to population number where the probability of infection during a single needle sharing act is 0.686. Initial recruitment and migration rates will be set at 1% and the other parameters and population numbers will be unchanged.

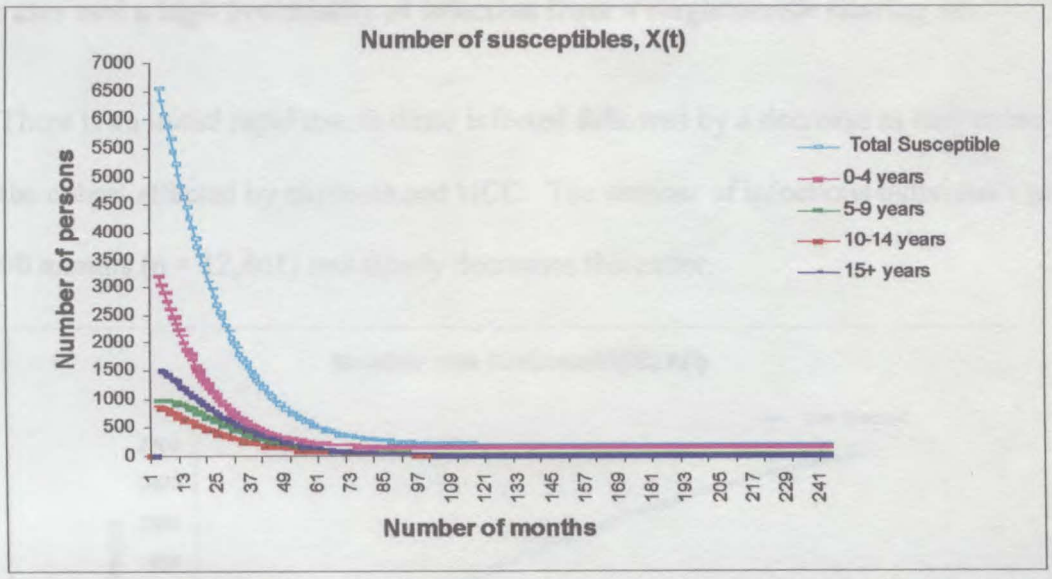

Figure 9. Number of susceptibles after 20 years, population 14,700, low infectivity rates and a high probability of infection from a single needle sharing act.

Figure 9 illustrates a rapid decline in the total susceptible population, with those in the 0 - 4 years injecting group in most rapid decline and those in the 10-14 years injecting group is the slowest. The population of susceptible IDU's is reduced by 50% after only 18 months. The higher probability of infection results in a rapid shift from the susceptible group into the infected population.

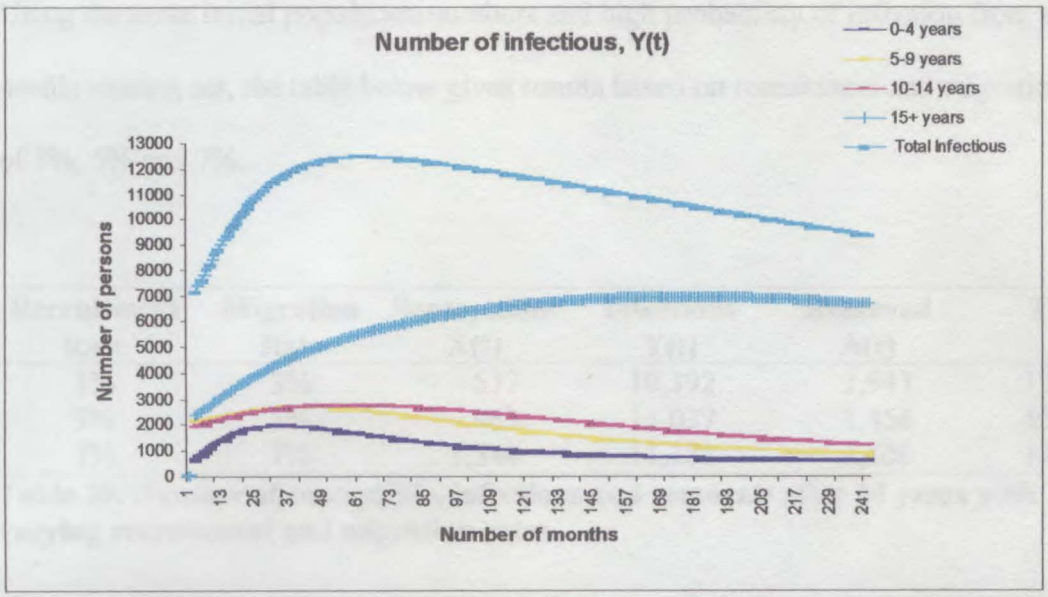

Figure 10. Number of infectious after 20 years, population 14,700, low infectivity rates and a high probability of infection from a single needle sharing act.

There is an initial rapid rise in those infected followed by a decrease as they move into the cohort affected by cirrhosis and HCC. The number of infectious individuals peaks at 60 months (n = 12,461) and slowly decreases thereafter.

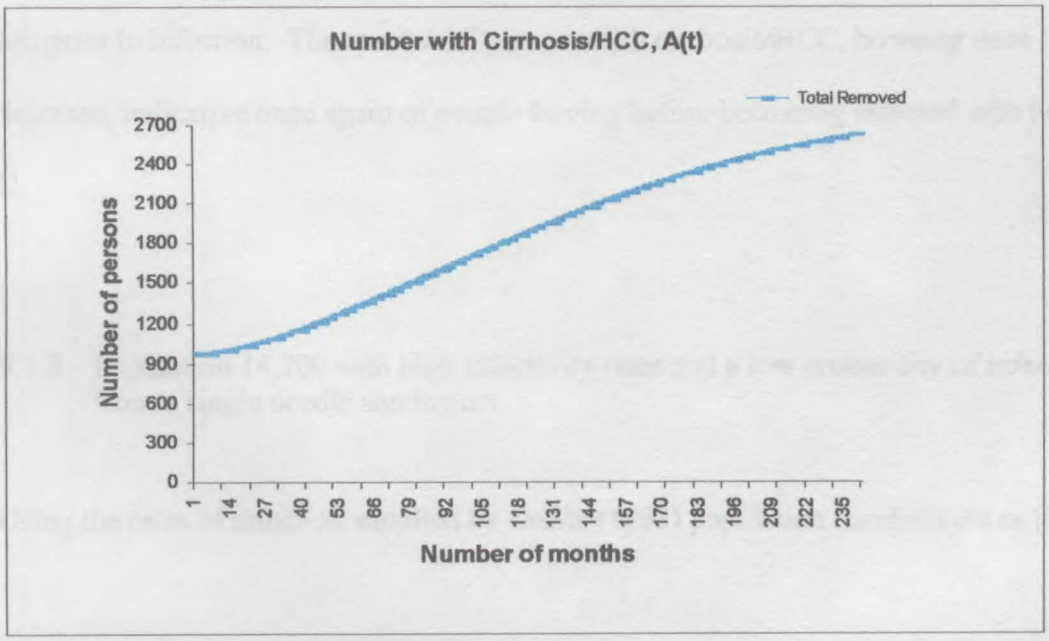

Figure 11. Number of removals after 20 years, population 14,700, low infectivity rates and a high probability of infection from a single needle sharing act.

Using the same initial population numbers and high probability of infection from a single needle sharing act, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	577	10,392	1,947	12,916
5%	5%	963	11,037	1,456	13,456
7%	7%	1,348	11,381	1,100	13,829

Table 39. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

The higher the recruitment rate the higher the number in the needle sharing but not infected cohort becomes. However, as the number of infectious increases this is due solely to weight of numbers rather than behaviour changes. Thus the infection rate appears to be a key parameter from a HCV control policy viewpoint. The increase in the number of infected persons is not great and reflects the number leaving intravenous drug use prior to infection. The number of persons with cirrhosis/HCC, however does decrease, indicative once again of people leaving before becoming infected with hepatitis C.

5.1.3 Population 14,700 with high infectivity rates and a low probability of infection from a single needle sharing act.

Using the rates of infection supplied by Crofts (1993) population numbers are as follows:

	0-4 years	5-9 years	10-14 years	15+ years
IVDU's that do not have HCV, X(t)	2,360	930	280	473
IVDU's who do have HCV, Y(t)	1,484	2,213	2,520	3,450
IVDU's with cirrhosis/HCC, A(t)	0	0	0	972
Rate of needle sharing per month, (n)	0.15	0.14	0.14	0.14
Parameters				
1% recruitment rate, (Λ)				147
Probability of transmission during single needle sharing act (β) (Rate of needle sharing*probability of infection)				0.182
Migration rate out of IVDU population, (μ)				1%
Mean incubation rate – 6 weeks, ($\frac{1}{\alpha}$)				0.6
Death rate due to HCC/cirrhosis				0.00625
Rate at which hepatitis C develops into cirrhosis				0.003

Table 40. Parameters: population 14,700 with high infectivity rates and a low probability of infection from a single needle sharing act.

Like Figure 6. The results here indicate a decline in the total susceptible population, with those in the 0 - 4 years injecting group in most rapid decline and those in the 10-14 years injecting group is the slowest. The population of susceptible IDU's is reduced by 50% after 71 months.

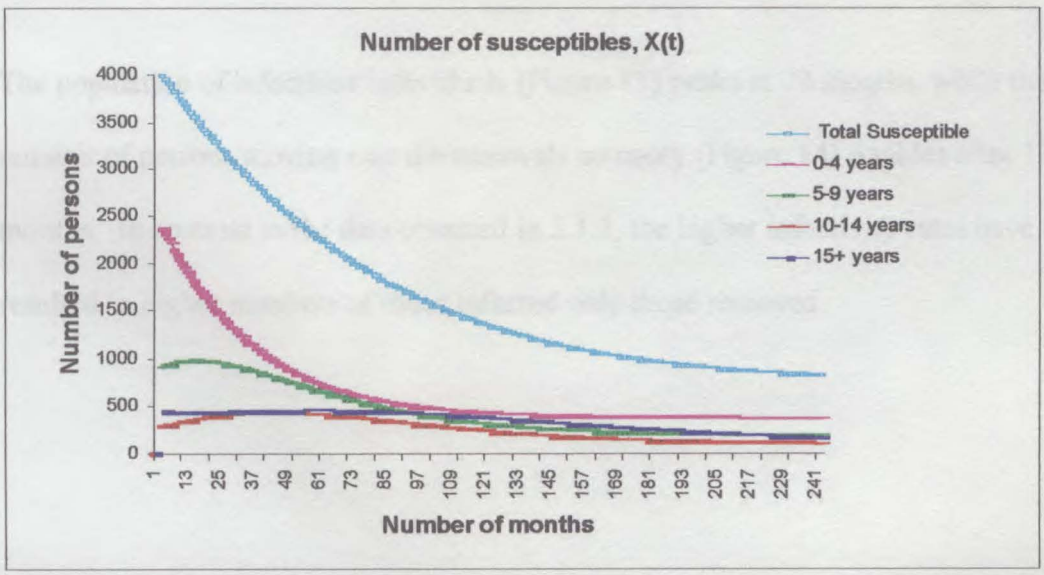

Figure 12. Number of susceptibles after 20 years, population 14,700, high infectivity rates and a low probability of infection from a single needle sharing act.

In this situation, where the higher infectivity rates suggested by Croft (1993) are used, after 20 years this IVDU population now numbers 12,200, with 822 not infected, but at risk, 8,806 infected and still needle sharing and with 2,572 persons having severe cirrhosis or HCC.

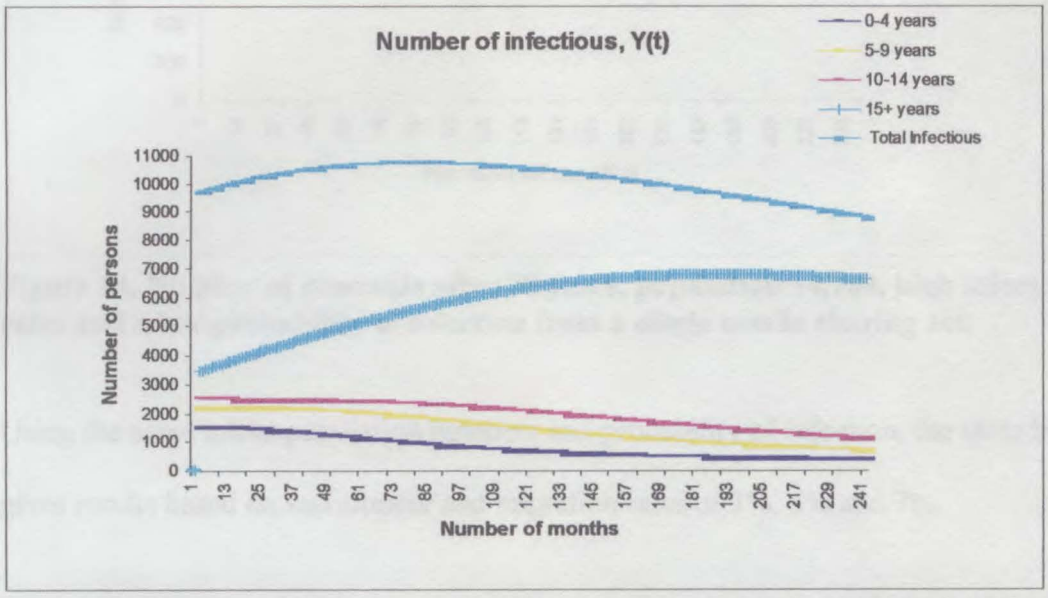

Figure 13. Number of infectious after 20 years, population 14,700, high infectivity rates and a low probability of infection from a single needle sharing act.

The population of infectious individuals (Figure 13) peaks at 78 months, while the number of persons moving into the removals category (Figure 14) doubles after 136 months. In contrast to the data obtained in 5.1.1, the higher infectivity rates have not resulted in higher numbers of those infected only those removed.

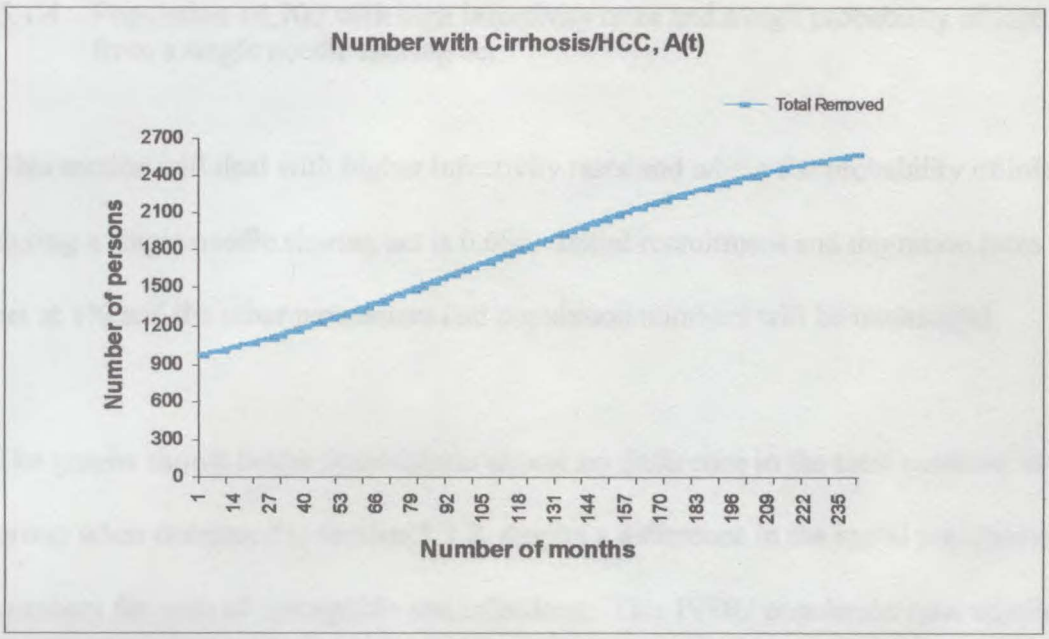

Figure 14. Number of removals after 20 years, population 14,700, high infectivity rates and a low probability of infection from a single needle sharing act.

Using the same initial population numbers and probability of infection, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	2,274	8,833	1,872	12,979
5%	5%	3,706	8,443	1,366	13,515
7%	7%	5,095	7,790	997	13,882

Table 41. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

These results once again demonstrate a movement into the IVDU population where each person is susceptible to infection and a corresponding movement out prior to infection with hepatitis C.

5.1.4 Population 14,700 with high infectivity rates and a high probability of infection from a single needle sharing act.

This section will deal with higher infectivity rates and where the probability of infection during a single needle sharing act is 0.686. Initial recruitment and migration rates will be set at 1% and the other parameters and population numbers will be unchanged.

The graphs shown below demonstrate almost no difference in the total numbers in each group when compared to section 5.1.2, despite a difference in the initial population numbers for each of susceptible and infectious. This IVDU population now numbers 12,116, with 192 not infected, but at risk, 9,289 infected and still needle sharing and with 2,634 persons having severe cirrhosis or HCC.

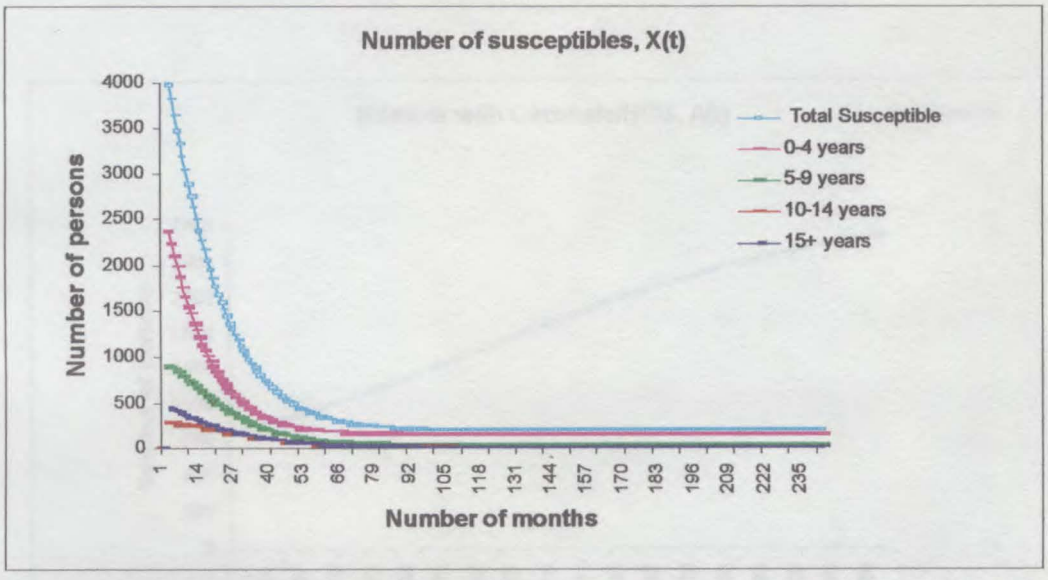

Figure 15. Number of susceptibles after 20 years, population 14,700, high infectivity rates and a high probability of infection from a single needle sharing act.

Like Figure 9, these results illustrates a rapid decline in the total susceptible population, with those in the 0 - 4 years injecting group in most rapid decline and those in the 10-14 years injecting group is the slowest. The population of susceptible IDU's is reduced by

50% after only 16 months. The higher probability of infection results in a rapid shift from the susceptible group into the infected population.

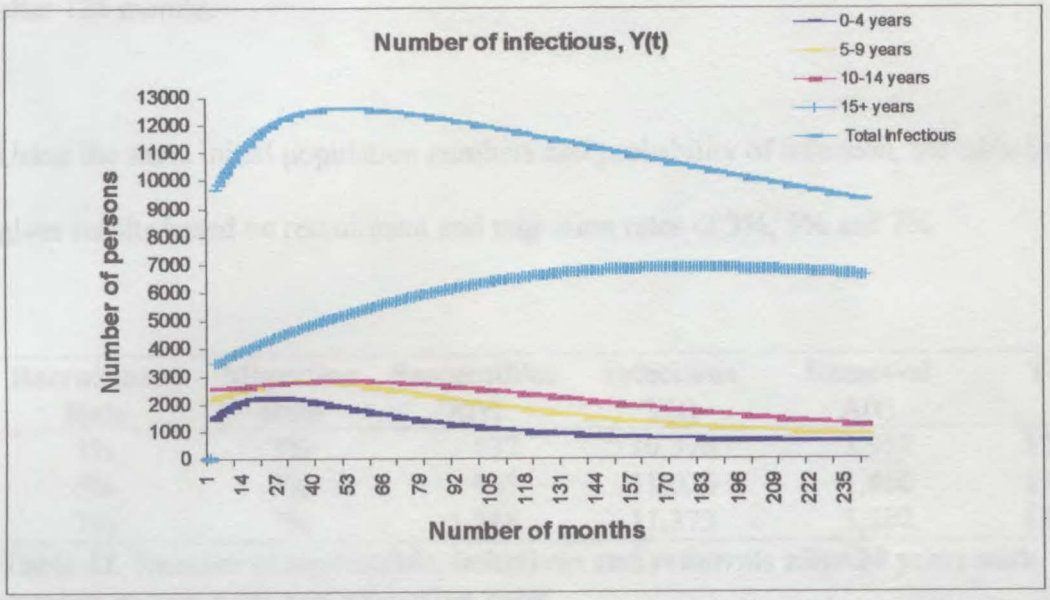

Figure 16. Number of infectious after 20 years, population 14,700, high infectivity rates and a high probability of infection from a single needle sharing act.

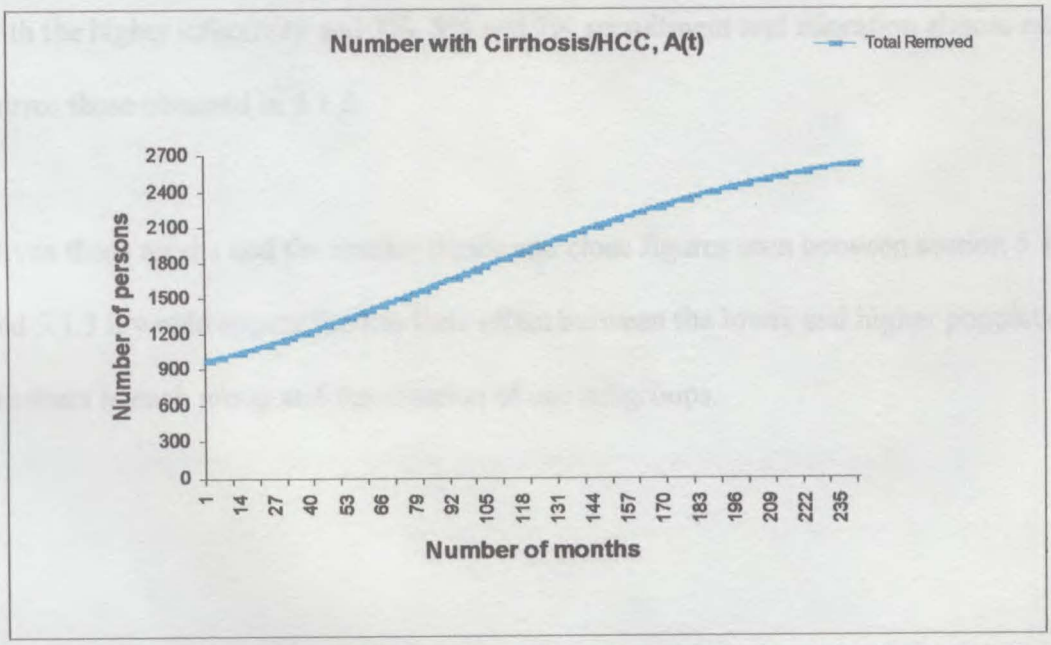

Figure 17. Number of susceptibles after 20 years, population 14,700, high infectivity rates and a high probability of infection from a single needle sharing act.

Figure 16 describes a corresponding rapid increase in the infectious population where the growth peaks at 48 months. Likewise the removals group (Figure 17) doubles in size after 126 months.

Using the same initial population numbers and probability of infection, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	577	10,376	1,952	12,905
5%	5%	963	11,026	1,460	13,449
7%	7%	1,348	11,373	1,102	13,823

Table 42. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

As with the data obtained for recruitment and migration rates of 1%, the results obtained with the higher infectivity and 3%, 5% and 7% recruitment and migration almost exactly mirror those obtained in 5.1.2.

Given these results and the similar trends and close figures seen between section 5.1.1. and 5.1.3 it would appear there is little effect between the lower and higher population numbers in each group and the duration of use subgroups.

5.2 Total Intravenous Drug Using population, 19,600.

5.2.1 Population 19,600 with low infectivity rates and a low probability of intection from a single needle sharing act.

Using the rates of infection supplied by the 1999 HIV/AIDS, Hepatitis C & Sexually Transmissible Infections in Australia: Annual Surveillance report population numbers are as follows:

	0-4 years	5-9 years	10-14 years	15+ years
IVDU's that do not have HCV, X(t)	4,254	1,321	1,157	2,009
IVDU's who do have HCV, Y(t)	871	2,940	2,576	3,175
IVDU's with cirrhosis/HCC, A(t)	0	0	0	1296
Rate of needle sharing per month, (n)	0.15	0.14	0.14	0.14
Parameters				
1% recruitment rate, (Λ)				196
Probability of transmission during single needle sharing act (β) (Rate of needle sharing*probability of infection)				0.182
Migration rate out of IVDU population, (μ)				1%
Mean incubation rate – 6 weeks, ($\frac{1}{\alpha}$)				0.6
Death rate due to HCC/cirrhosis				0.00625
Rate at which hepatitis C develops into cirrhosis				0.003

Table 43. Parameters: Population 19,600 with low infectivity rates and a low probability of infection from a single needle sharing act.

Figure 18 illustrates a decline in the total susceptible population, with those in the 0 - 4 years injecting group in most rapid decline and those in the 10-14 years injecting group is the slowest. The population of susceptible IDU's is reduced by 50% after 75 months.

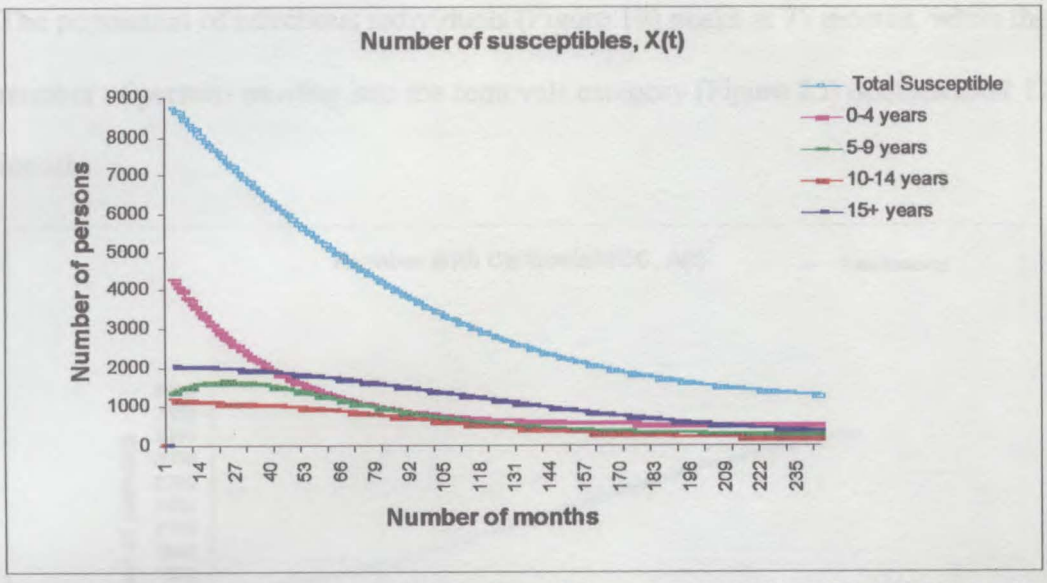

Figure 18. Number of susceptibles after 20 years, population 19,600, low infectivity rates and a low probability of infection from a single needle sharing act.

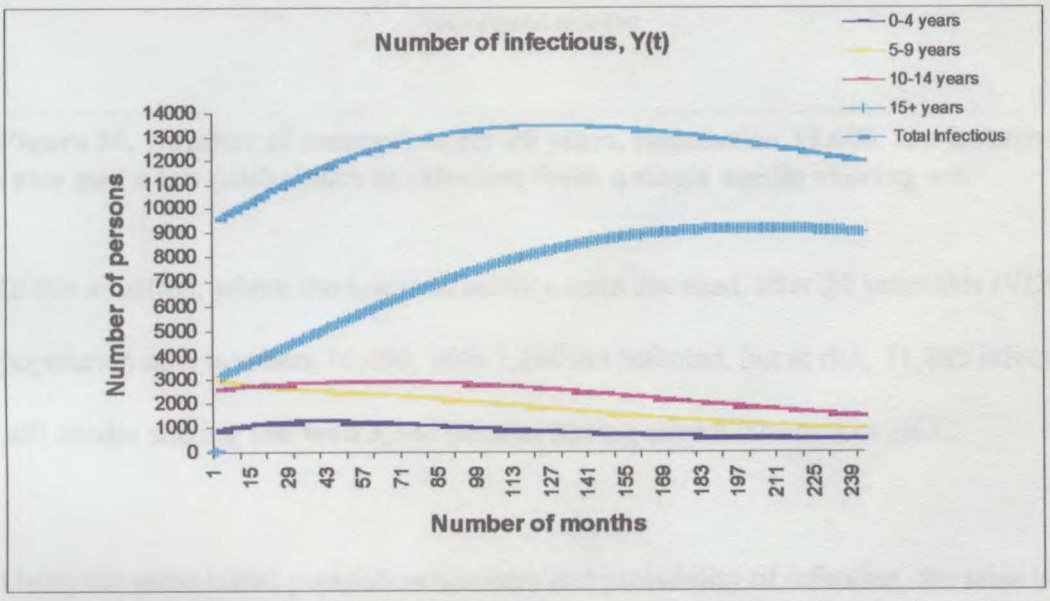

Figure 19. Number of infectious after 20 years, population 19,600, low infectivity rates and a low probability of infection from a single needle sharing act.

The population of infectious individuals (Figure 19) peaks at 75 months, while the number of persons moving into the removals category (Figure 20) doubles after 124 months.

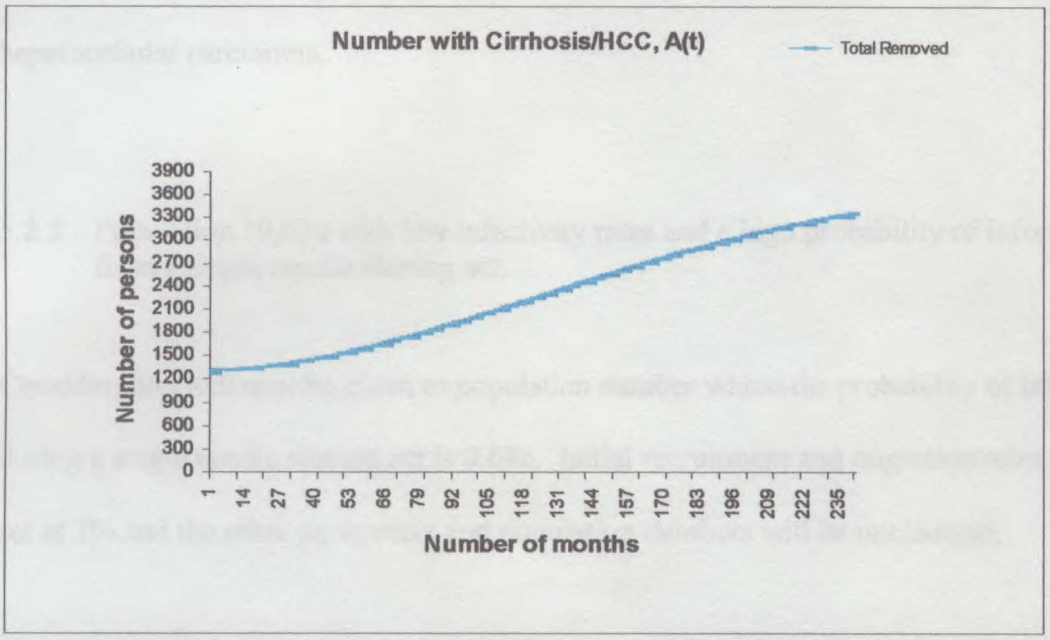

Figure 20. Number of removals after 20 years, population 19,600, low infectivity rates and a low probability of infection from a single needle sharing act.

In this situation, where the lower infectivity rates are used, after 20 years this IVDU population now numbers 16,496, with 1,260 not infected, but at risk, 11,889 infected and still needle sharing and with 3,347 persons having severe cirrhosis or HCC.

Using the same initial population numbers and probability of infection, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	3,232	11,810	2,427	17,467
5%	5%	5,175	11,198	1,763	18,136
7%	7%	7,059	10,254	1,280	18,594

Table 44. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

As the recruitment rate increases among this cohort the number of susceptible IDU's increases. The corresponding migration rate show a movement out of the drug using population and a smaller number of people suffering ill effects from cirrhosis and hepatocellular carcinoma.

5.2.2 Population 19,600 with low infectivity rates and a high probability of infection from a single needle sharing act.

Consideration will now be given to population number where the probability of infection during a single needle sharing act is 0.686. Initial recruitment and migration rates will be set at 1% and the other parameters and population numbers will be unchanged.

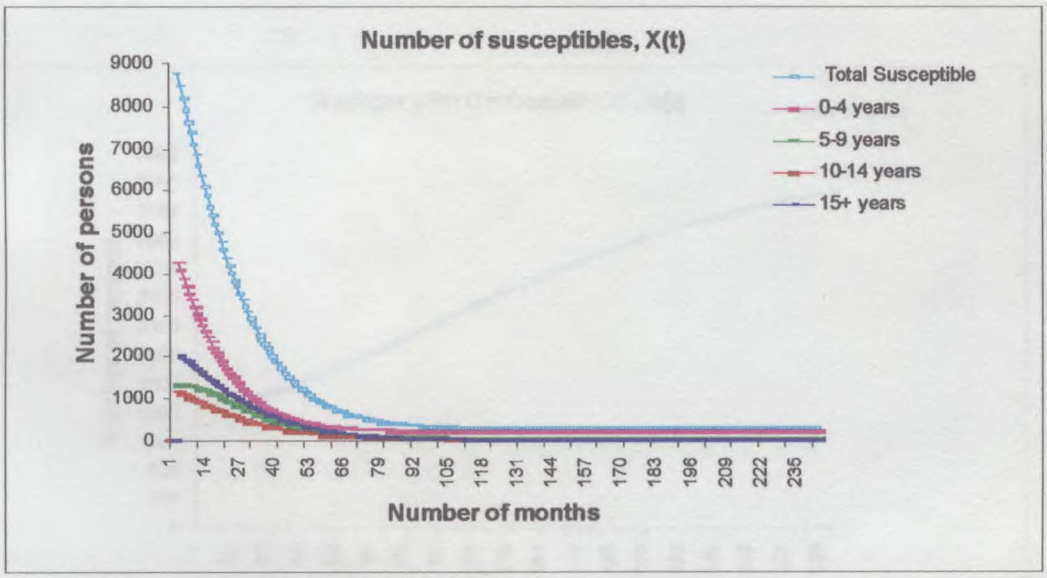

Figure 21. Number of susceptibles after 20 years, population 19,600, low infectivity rates and a high probability of infection from a single needle sharing act.

Once again the higher probability of infection results in a rapid shift from the susceptible group into the infected population. The population of susceptible individuals decreases by 50% after only 18 months.

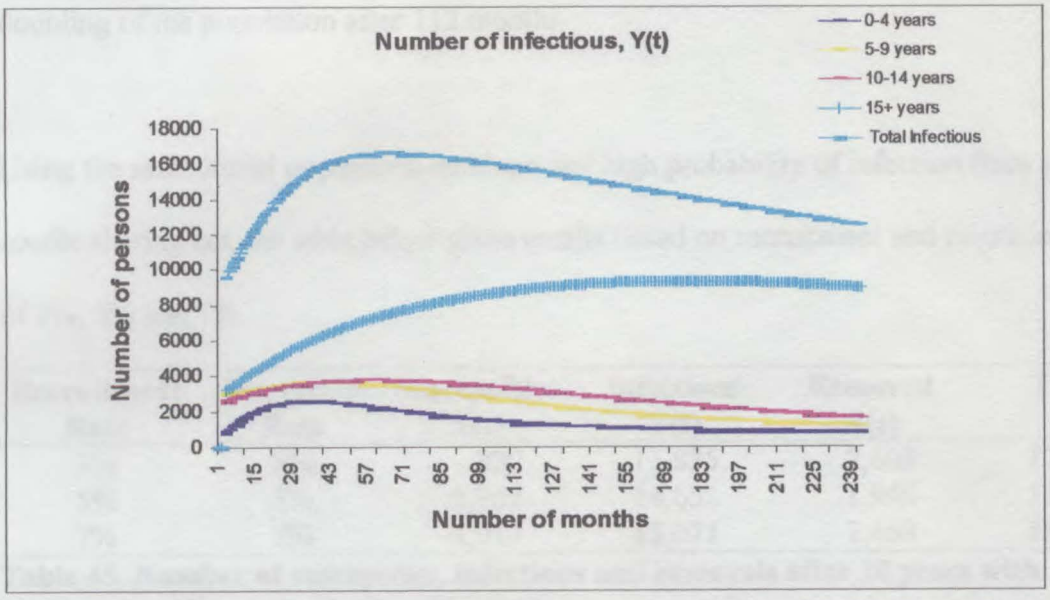

Figure 22. Number of infectious after 20 years, population 19,600, low infectivity rates and a high probability of infection from a single needle sharing act.

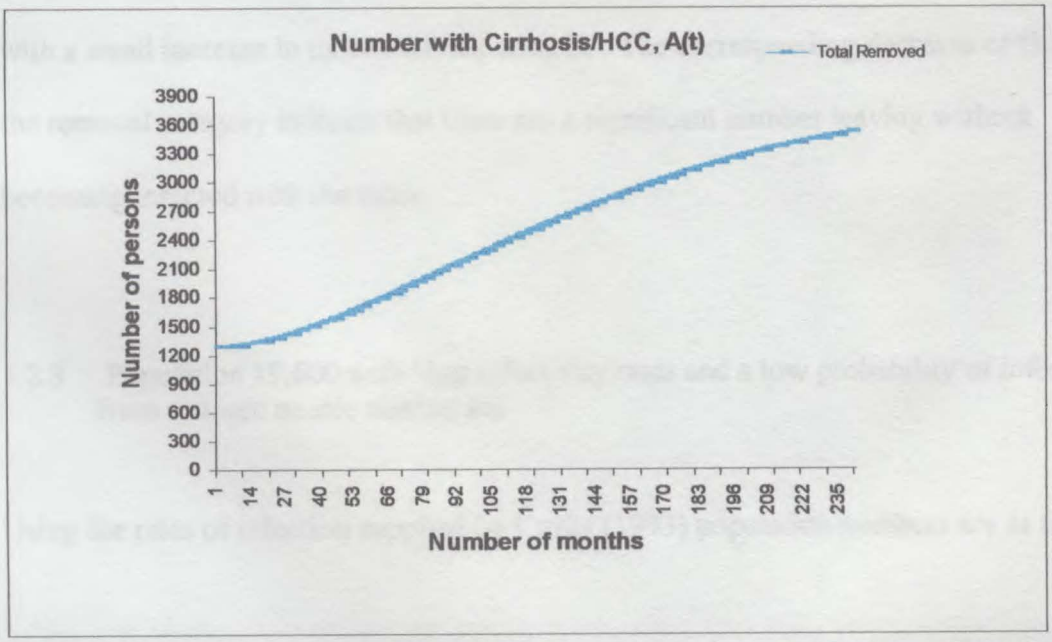

Figure 23. Number of removals after 20 years, population 19,600, low infectivity rates and a high probability of infection from a single needle sharing act.

Figure 22 demonstrates a rapid increase in the number of infectious individuals, with the population peaking after 60 months and then decreasing slightly as they move into the removals group. Figure 23 shows a steady increase in the number of removals, with a doubling of the population after 112 months.

Using the same initial population numbers and high probability of infection from a single needle sharing act, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	820	13,835	2,603	17,257
5%	5%	1,367	14,652	1,946	17,965
7%	7%	1,914	15,071	1,468	18,454

Table 45. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

Once more results indicate a rapid increase in the number of IDU's that are not infected, with a small increase in those with hepatitis C. The corresponding decrease of those in the removal category indicate that there are a significant number leaving without becoming infected with the virus.

5.2.3 Population 19,600 with high infectivity rates and a low probability of infection from a single needle sharing act.

Using the rates of infection supplied by Crofts (1993) population numbers are as follows:

	0-4 years	5-9 years	10-14 years	15+ years
IVDU's that do not have HCV, X(t)	3,147	1,240	373	583
IVDU's who do have HCV, Y(t)	1,978	3,021	3,360	4,601
IVDU's with cirrhosis/HCC, A(t)	0	0	0	1296
Rate of needle sharing per month, (n)	0.15	0.14	0.14	0.14
Parameters				
1% recruitment rate, (Λ)				196
Probability of transmission during single needle sharing act (β) (Rate of needle sharing*probability of infection)				0.182
Migration rate out of IVDU population, (μ)				1%
Mean incubation rate – 6 weeks, ($\frac{1}{\alpha}$)				$0.\overline{6}$
Death rate due to HCC/cirrhosis				0.00625
Rate at which hepatitis C develops into cirrhosis				$0.00\overline{3}$

Table 46. Parameters: Population 19,600 with high infectivity rates and a low probability of infection from a single needle sharing act.

Figure 24 illustrates a decline in the total susceptible population, with those in the 0 - 4 years injecting group in most rapid decline and those in the 10-14 years injecting group is the slowest. The population of susceptible IDU's is reduced by 50% after 71 months.

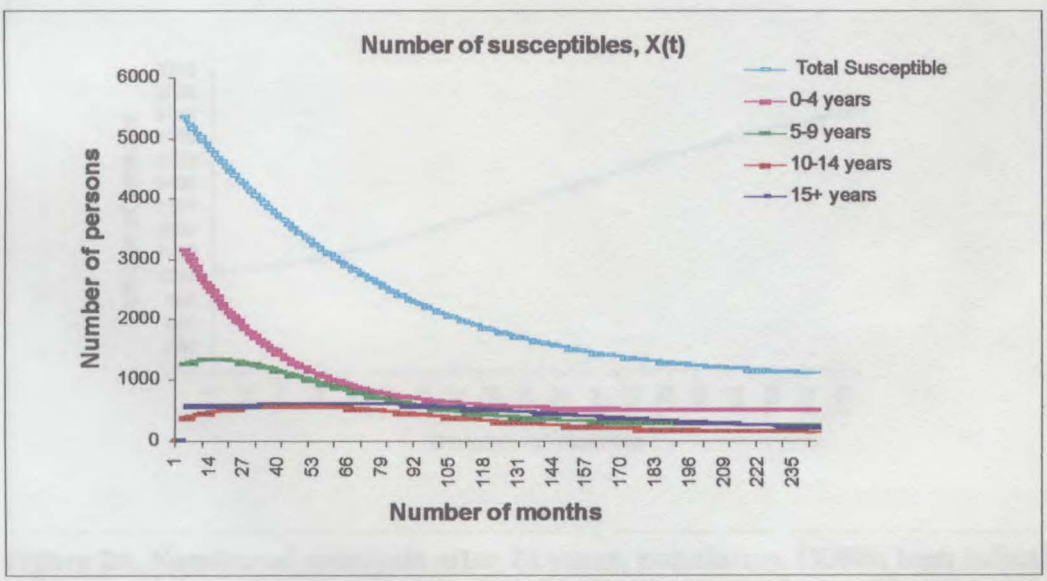

Figure 24. Number of susceptibles after 20 years, population 19,600, high infectivity rates and a low probability of infection from a single needle sharing act.

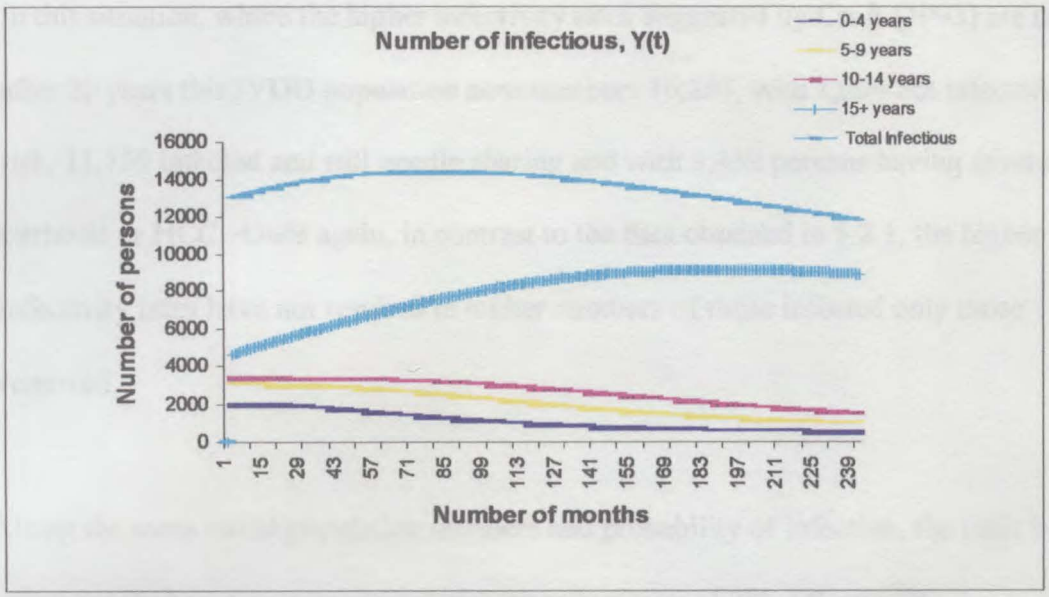

Figure 25. Number of infectious after 20 years, population 19,600, high infectivity rates and a low probability of infection from a single needle sharing act.

The population of infectious individuals (Figure 25) peaks at 78 months, while the number of persons moving into the removals category (Figure 26) doubles after 124 months.

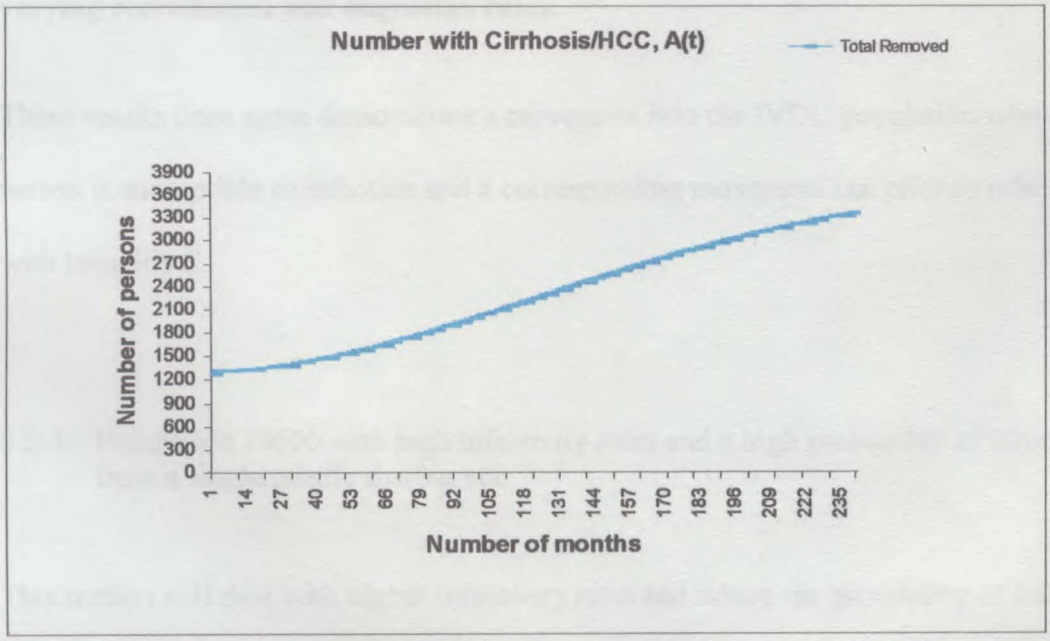

Figure 26. Number of removals after 20 years, population 19,600, high infectivity rates and a low probability of infection from a single needle sharing act.

In this situation, where the higher infectivity rates suggested by Croft (1993) are used, after 20 years this IVDU population now numbers 16,285, with 1,094 not infected, but at risk, 11,759 infected and still needle sharing and with 3,432 persons having severe cirrhosis or HCC. Once again, in contrast to the data obtained in 5.2.1, the higher infectivity rates have not resulted in higher numbers of those infected only those removed.

Using the same initial population numbers and probability of infection, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	3,029	11,791	2,498	17,318
5%	5%	4,937	11,268	1,822	18,028
7%	7%	6,789	10,396	1,331	18,516

Table 47. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

These results once again demonstrate a movement into the IVDU population where each person is susceptible to infection and a corresponding movement out prior to infection with hepatitis C.

5.2.4 Population 19600 with high infectivity rates and a high probability of infection from a single needle sharing act.

This section will deal with higher infectivity rates and where the probability of infection during a single needle sharing act is 0.686. Initial recruitment and migration rates will be set at 1% and the other parameters and population numbers will be unchanged.

This IVDU population now numbers 16,176, with 256 not infected, but at risk, 12,407 infected and still needle sharing and with 3,513 persons having severe cirrhosis or HCC.

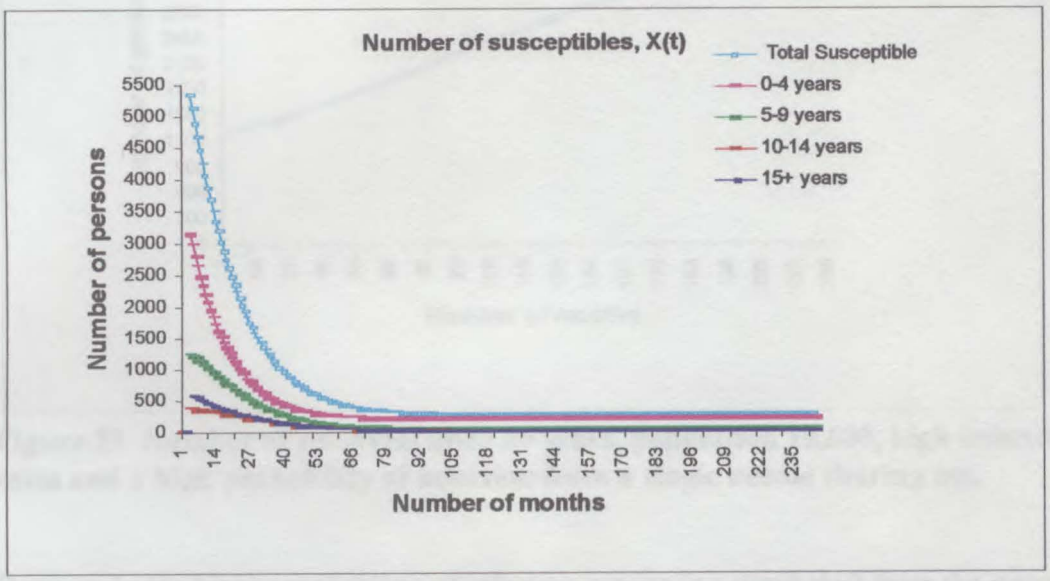

Figure 27. Number of susceptibles after 20 years, population 19,600, high infectivity rates and a high probability of infection from a single needle sharing act.

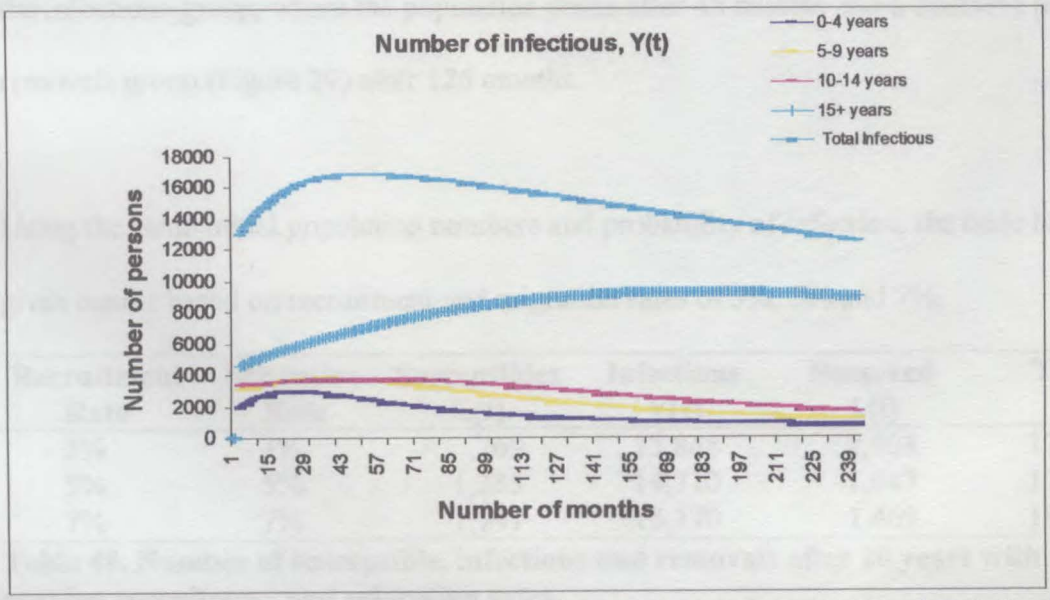

Figure 28. Number of infectious after 20 years, population 19,600, high infectivity rates and a high probability of infection from a single needle sharing act.

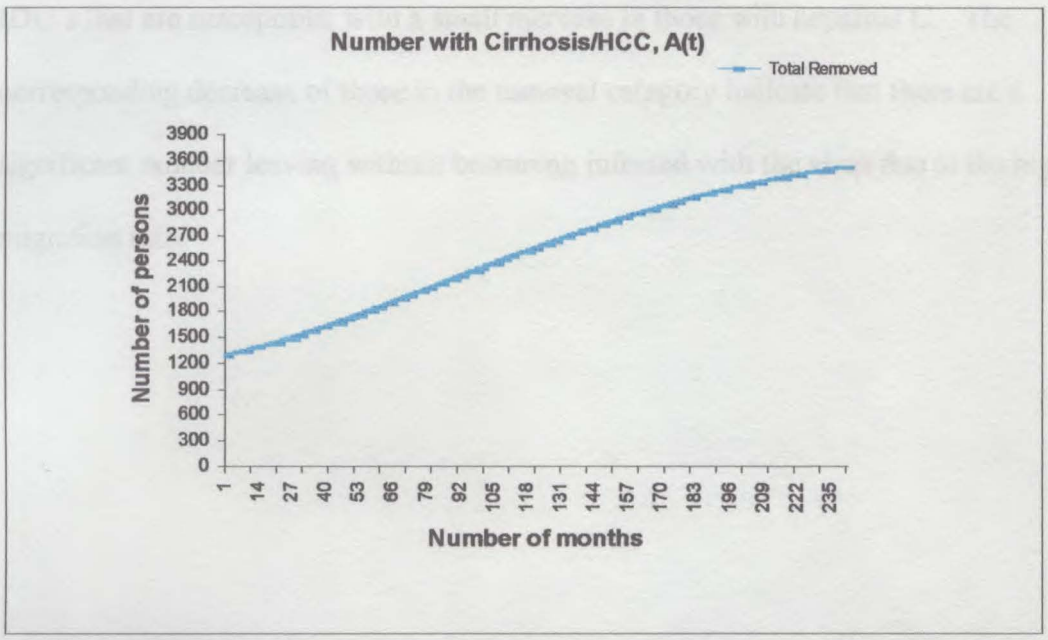

Figure 29. Number of removals after 20 years, population 19,600, high infectivity rates and a high probability of infection from a single needle sharing act.

Once again the higher probability of infection results in a rapid shift from the susceptible group (Figure 27) into the infected population. The population of susceptible individuals decreases by 50% after only 18 months. Figure 28 indicates a corresponding shift into the infectious group, where the population peaks after 48 months and a doubling of the removals group (Figure 29) after 126 months.

Using the same initial population numbers and probability of infection, the table below gives results based on recruitment and migration rates of 3%, 5% and 7%.

Recruitment Rate	Migration Rate	Susceptibles X(t)	Infectious Y(t)	Removed A(t)	Total
3%	3%	769	13,848	2,603	17,221
5%	5%	1,283	14,710	1,947	17,940
7%	7%	1,797	15,170	1,469	18,436

Table 48. Number of susceptible, infectious and removals after 20 years with varying recruitment and migration rates.

As with previous simulations these results indicate a rapid increase in the number of IDU's that are susceptible, with a small increase in those with hepatitis C. The corresponding decrease of those in the removal category indicate that there are a significant number leaving without becoming infected with the virus due to the higher migration rate.

TREATMENT COSTS

6.1 Treatment costs from other research.

Models on the costs and the effects of treatment with α-Interferon have increased in frequency in recent years as the efficacy of different treatment protocols are better understood. Three such studies examine the Australian situation, one examines treatment costs in Britain, while the majority of others originate from the United States of America.

Sheill et al (1994), used a Markov modelling process to simulate the costs and outcomes of a hypothetical cohort of patients with hepatitis C, who were treated both with and without α-Interferon. In this model, treatment costs ranged from $33,230 per life-year gained in those with cirrhosis at the commencement of treatment and $71,950 per life-year gained in those with advanced liver disease. Sheill concluded that little was known at this time of the long term impact of α-Interferon on the disease and given the expense of the treatment further monitoring should be undertaken as to the cost-effectiveness of the treatment regime.

Dushieko and Roberts (1995) undertook a study on the treatment costs with α-Interferon associated with chronic hepatitis B and C. Once again a hypothetical cohort of patients with hepatitis B or C were either treated with α-Interferon or were part of a control group. A transitional probability model was employed, with two rates of progression, two mortality rates and discounted and undiscounted costs employed. (Discounting is the process where costs and benefits occurring at different points in time are made

commensurate with each other). Mortality rates in the treatment group was lower with 13 to 22 lives saved in the hepatitis C group and fewer patients progressed to cirrhosis. Discounted costs per year of life saved ranged from £2,142 to £17,128.

The following treatment assumptions were used for this model. Patients with chronic hepatitis C were treated with 3milliunits of α-Interferon three times a week for 26 weeks. An initial response rate of 50% was assumed, with a 50% relapse rate and a final response rate of 25%. Patients with chronic hepatitis and without cirrhosis were seen twice yearly, where the initial visit included an extensive testing regime including liver biopsy. Patients with cirrhosis were seen four times a year and those with decompensating (severe) cirrhosis were seen every 2 months. This final group of patients were assumed to require at least one hospital admission per year lasting an average of seven days. Finally it was assumed that 20% of the decompensating group would undergo a liver transplant , with a survival rate of 80% after 2 years. The model projected the natural history of these patients over a 30-year period.

In an editorial by Koff and Seeff (1995) limitations of this model were raised. Most notably, concerns over the author's assumption that natural course of hepatitis C would mirror that of hepatitis B was raised, given the lack of published data to that effect. They rightly suggest that a series of rates should have been employed in the hepatitis C model. The duration of the model was also questioned, given that many acquire the infection in adolescence or early adulthood and longer period may have been more appropriate. Subsequent models have however, continued to use the thirty year period for their models. Finally Koff and Seeff question the α-Interferon response rates employed by

Dushieko and Roberts as no meta-analysis treatment trials were cited, nor a primary data set analysed. They suggest the response rate of 25% was too high and that 5% to 20% was more reasonable. They also suggest that further relapse among these responders should be expected at a later time. Despite these reservations the Dushieko model has continued to be used as a template for further models.

From the United States, Wong et al (1999) concluded that liver biopsy prior to the commencement of α-Interferon treatment increased the costs of managing patients with chronic hepatitis C without improvement to health outcomes. HCV RNA testing would miss 36% of sustained responders resulting in marginal cost-effectiveness ratios up to US$4,400. Treatment with α-Interferon produced a marginal cost-effectiveness ratio of US$12,400 and reached all potential sustained responders. Wong (1999), in another article, projected a US$400 reduction in lifetime cost of care and a 1.5 year increase in life expectancy associated with α-Interferon treatment. Kim et al (2001) identified hospital admissions for diagnoses associated with hepatitis C from a national inpatient database. For the year 1995, they estimated 26,700 admissions and 2,600 deaths in the United States resulting in total cost of US$514 million. Highest hospital charges resulted from liver transplant and patient death, with the complications of cirrhosis, variceal bleeding, ecephalopathy and hepatorenal syndrome adding significantly to costs and risk of death.

Brown and Crofts (1998) used a Markov model to simulate the progress of hepatitis C and estimate the direct health care costs of treating intravenous drug users in Australia. Once again they use the hypothetical cohort of 1000 patients as they develop and

progress through the sequelae of hepatitis C over time. The cohort were grouped into a limited number of disease states and direct medical costs were employed for ambulatory visits and hospital admissions over the course of the disease. Costs associated with every 1000 newly infected hepatitis C patients resulted in $14.32 million dollars in treatment over the years as symptoms progress, with a resultant cummulative cost of $0.5 billion after 60 years (1994 dollars) as successive cohorts are added to the pool. A total cost of $4 billion would be needed if the current estimate of 10,000 new hepatitis C infections per year among IVDU's was to continue. An emphasis was placed on intervention prior to infection as a strategy to reduce health costs.

Sheill et al (1999) re-evaluated their economic evaluation of treatment with α-Interferon undertaken in 1994. The authors cite charges in clinical practice, cost reductions in the production of α-Interferon and extension of the treatment schedule from 6 months to 12 months as motivators for this evaluation.

A Markov model was employed to simulate the costs and effects of 6 months and 12 months treatment as opposed to no treatment. Their hypothetical cohort consisted of 1000 patients with chronic hepatitis C aged 40 years at the commencement of treatment. As part of their re-evaluation they included meta-analyses on the impact of α-Interferon on the natural history of hepatitis C. Current treatment regimes now discontinue the use of α-Interferon if no response is observed after 12 weeks. Additionally, studies have indicated increased benefits of treatment for a period of 12 months rather 6 months and this practice has now been adopted in Australia. The cohort were divided as follows:

	Percentage	Range
Disease transition probabilities		
From chronic infection to cirrhosis	20%	10% - 30%
From cirrhosis to advanced liver failure	20%	10% - 30%
From cirrhosis to hepatocellular carcinoma	14%	7% - 21%
Effectiveness of treatment		
Long term response after 6 months	18%	14% - 24%
Long term response after 12 months	35%	26% - 38%
Discontinue treatment after 12 weeks because of lack of response	26%	13% - 39%

Table 49. Division into disease stages of the Sheill (1999) cohort.

All subjects with advanced liver failure or hepatocellular carcinoma were assumed to die within 2 years of diagnosis. Treatment costs were calculated using the Medical Benefits Schedule for 1996 and included medical management of chronic infection, treatment with iα-Interferon for 6 and 12 months, management of compensated cirrhosis, ascites, variceal haemorrhage, hepatic encphalopathy, hepatocellular carcinoma and other hospital admissions including transplant and terminal care. Associated costs are listed below. It was assumed that 2% of patients experiencing cirrhosis would undergo a liver transplant each year and that 25% of patients would experience at least one episode of septicaemia, requiring hospital admission.

	Cost ($)	Range ($)
Medical management of chronic infection	405	200 – 600
Treatment with α-Interferon		
6 months' treatment including discontinuing treatment	2,800	1,975 – 3,630
12 months' treatment including discontinuing treatment	5,150	3,620 – 6,670
Cirrhosis (weighted average estimated proportion of patients likely to experience each state of cirrhosis)	2,825	1,400 – 4,200
Management of compensated cirrhosis	660	330 – 990
Diuretic-sensitive ascites	1,880	940 – 2,820
Refractory ascites	13,640	6,820 – 20,460
Variceal haemorrhage (Year 1)	5,850	2,925 – 8,775
Hepatic Encephalopathy (Year 1)	6,375	3,190 – 9,565
Hepatocellular carcinoma (Year 1)	8,865	4,435 – 13,290
Liver Transplant (Year 1)	92,525	46,265 – 138,790
Septicaemia	5,300	2,650 – 7,950
Terminal Care	28,400	14,200 – 42,600

Table 50. Cost of medical care, per individual, for the Sheill (1999) cohort.

6.2 Treatment costs in 20 years time for hepatitis C in Western Australia.

Treatment costs utilised by Shiell et al were based on the Medical Benefits Schedule for 1996. In order to project the costs twenty years from this current work, an inflationary rate will be applied to the figures for a period of 27 years in order to model the costs 20 years following the current simulation. The Australian Bureau of Statistics indicates a rise in health costs nationally for the twelve months to March 2003 of 7.2%, with most increases due to a rise in pharmaceutical costs (11.8%). Additional Consumer Price Index information shows an overall percentage change in the CPI for Perth ranging from 1.8% in 1998-99 to 2.8% in 2001-02. Taking a conservative approach, an inflationary rate of 1%, 2% and 3% will be applied.

	1996	2023		
		1%	2%	3%
	Cost ($)	Cost ($)	Cost ($)	Cost ($)
Medical management of chronic infection	405	530	691	900
Treatment with α-Interferon				
6 months' treatment including discontinuing treatment	2,800	3,663	4,779	6,220
12 months' treatment including discontinuing treatment	5,150	6,737	8,790	11,440
Cirrhosis (weighted average – estimated proportion of patients likely to experience each state of cirrhosis)	2,825	3,696	4,822	6,275
Management of compensated cirrhosis	660	863	1,127	1,466
Diuretic-sensitive ascites	1,880	2,459	3,209	4,176
Refractory ascites	13,640	17,844	23,282	30,298
Variceal haemorrhage (Year 1)	5,850	7,653	9,985	12,995
Hepatic Encephalopathy (Year 1)	6,375	8,340	10,881	14,161
Hepatocellular carcinoma (Year 1)	8,865	11,597	15,132	19,692
Liver Transplant (Year 1)	92,525	121,042	157,930	205,525
Septicaemia	5,300	6,934	9,046	11,773
Terminal Care	28,400	37,153	48,476	63,085

Table 51. Undiscounted medical costs of hepatic disease in 20 years, using inflationary rates of 1%, 2% and 3%.

If a 3% discount is applied to the figures the costs will then be:

	1996	2023		
	Cost ($)	1% Cost ($)	2% Cost ($)	3% Cost ($)
Medical management of chronic infection	405	514	671	873
Treatment with α-Interferon				
6 months' treatment including discontinuing treatment	2,800	3,553	4,636	6,033
12 months' treatment including discontinuing treatment	5,150	6,535	8,527	11,096
Cirrhosis (weighted average – estimated proportion of patients likely to experience each state of cirrhosis)	2,825	3,585	4,677	6,087
Management of compensated cirrhosis	660	838	1,093	1,422
Diuretic-sensitive ascites	1,880	2,386	3,113	4,051
Refractory ascites	13,640	17,309	22,583	29,389
Variceal haemorrhage (Year 1)	5,850	7,423	9,686	12,605
Hepatic Encephalopathy (Year 1)	6,375	8,090	10,555	13,736
Hepatocellular carcinoma (Year 1)	8,865	11,249	14,678	19,101
Liver Transplant (Year 1)	92,525	117,411	153,192	199,359
Septicaemia	5,300	6,726	8,775	11,420
Terminal Care	28,400	36,039	47,021	61,192

Table 52. Discounted medical costs of hepatic disease in 20 years, using inflationary rates of 1%, 2% and 3%.

From the previous chapter, the expected number of people with hepatitis C (Infectious group) range from 7,677 to 11,381 for an initial population of 14,700 and 10,254 to 15,170 where the initial population is 19,600. Among this group most will require baseline treatment for hepatitis C, and 20% will have developed cirrhosis and will required additional care. This cohort will be given α-Interferon as a treatment regime, 25% of all those with cirrhosis will have one hospital admission for septicaemia and 2% will undergo a liver transplant.

The number of people (removals group) suffering severe symptoms and requiring terminal care range from 958 to 2,634 where the initial population is 14,700 and 1,280 to 3,513 for an initial population of 19,600. These patients will all require terminal care and it is assumed that this group will also require one admission for either management of

compensated cirrhosis, ascites, variceal haemorrhage, hepatic encphalopathy, hepatocellular carcinoma or septicaemia.

The proportion of people for each treatment and diagnostic/disease category are given in the table below.

Initial population	14,700		19,600	
	Best Case	Worst Case	Best Case	Worst Case
Infectious	7,677	11,381	10,254	15,170
α-Interferon Therapy				
26% discontinue after 12 weeks	1,996	2,959	2,666	3,944
18% long term response after 6 months	1,382	2,049	1,846	2,731
35% long term response after 12 months	2,687	3,983	3,589	5,310
No response	4,990	7,398	6,665	9,861
20% of non-responders develop cirrhosis	998	1,480	1,333	1,972
25% admission for septicaemia	250	370	333	493
2% liver transplant	20	30	27	39
Severe cirrhosis and HCC	958	2,634	1,280	3,513
14% with HCC	134	369	179	492

Table 53. Division into disease stages for best and worst case scenario from simulation.

An overall cost of a 12-week course is not given. In this simulation the number of patients receiving α-Interferon are charged at half the cost of those receiving a six-month course. Among those people with severe cirrhosis and expecting to have one hospital admission, a range is calculated from the least to the most costly options, not including management of HCC or liver transplant.

The table below shows predicted costs for the best case scenario (that is the lowest numbers in the infectious and removal groups) where the initial population is 14,700 persons. It includes non discounted and discounted rates. Total treatment costs for this

cohort range from $74,396,230 for the discounted group with only a 1% average rise in the CPI to $151,643,043 undiscounted and with an average rise in the CPI of 3%.

	Number of persons	1% CPI increase	2% CPI increase	3% CPI increase
Undiscounted Costs				
Basic management for HCV	7,677	$4,067,436	$5,307,026	$6,906,398
26% discontinue after 12 weeks	1,996	$3,655,659	$4,769,724	$6,207,170
18% long term response after 6 months	1,382	$5,061,732	$6,604,299	$8,594,629
35% long term response after 12 months	2,687	$18,102,723	$23,619,541	$30,737,736
20% of non-responders develop cirrhosis	998	$3,688,336	$4,812,359	$6,262,654
25% admission for septicaemia	250	$1,729,927	$2,257,124	$2,937,351
2% liver transplant	20	$2,416,023	$3,152,308	$4,102,315
Severe cirrhosis and HCC- 1 admission	958	$827,154 - $17,094,522	$1,079,230 - $22,304,090	$1,404,477 - $29,025,850
14% with HCC	134	$1,555,426	$2,029,443	$2,641,054
Terminal care		$35,592,701	$46,439,602	$60,435,054
Total Costs		**$76,697,145 - $89,308,854**	**$100,070,702 - $116,525,791**	**$130,228,902 - $151,643,043**
3% Discounted Costs				
Basic management for HCV	7,677	$3,945,440	$5,147,815	$6,699,207
26% discontinue after 12 weeks	1,996	$3,545,899	$4,626,632	$6,020,955
18% long term response after 6 months	1,382	$4,909,880	$6,406,170	$8,336,790
35% long term response after 12 months	2,687	$17,559,641	$22,910,955	$29,815,604
20% of non-responders develop cirrhosis	998	$3,577,686	$4,667,988	$6,074,774
25% admission for septicaemia	250	$1,678,030	$2,189,410	$2,849,230
2% liver transplant	20	$2,343,542	$3,057,739	$3,979,246
Severe cirrhosis and HCC- 1 admission	958	$802,340 - $16,581,687	$1,046,853 - $21,634,968	$1,362,342 - $28,155,074
14% with HCC	134	$1,508,763	$1,968,560	$2,561,823
Terminal care		$34,524,920	$45,046,414	$58,622,003
Total Costs		**$74,396,230 - $86,629,588**	**$97,068,535 - $113,030,018**	**$126,321,974 - $147,093,752**

Table 54. Costs for medical care for best case scenario for population 14,700.

	Number of persons	1% CPI increase	2% CPI increase	3% CPI increase
Undiscounted Costs				
Basic management for HCV	11,381	$6,029,934	$7,867,560	$10,238,599
26% discontinue after 12 weeks	2,959	$5,419,496	$7,071,091	$9,202,098
18% long term response after 6 months	2,049	$7,503,918	$9,790,747	$12,741,367
35% long term response after 12 months	3,983	$26,836,927	$35,015,500	$45,568,084
20% of non-responders develop cirrhosis	1,480	$5,467,884	$7,134,226	$9,284,260
25% admission for septicaemia	370	$2,564,583	$3,346,141	$4,354,564
2% liver transplant	30	$3,581,706	$4,673,234	$6,081,601
Severe cirrhosis and HCC- 1 admission	2,634	$2,274,243 - $46,804,731	$2,967,320 - $61,324,608	$3,861,578 - $79,805,938
14% with HCC	369	$4,276,610	$5,579,910	$7,261,521
Terminal care		$97,861,350	$127,684,667	$166,164,857
Total Costs		**$161,816,651 - $201,123,927**	**$211,130,391 - $262,416,588**	**$274,758,529 - $341,500,791**
3% Discounted Costs				
Basic management for HCV	11,381	$5,849,036	$7,631,534	$9,931,441
26% discontinue after 12 weeks	2,959	$5,256,911	$6,858,959	$8,926,035
18% long term response after 6 months	2,049	$7,278,800	$9,497,020	$12,359,126
35% long term response after 12 months	3,983	$26,031,819	$33,965,035	$44,201,041
20% of non-responders develop cirrhosis	1,480	$5,303,848	$6,920,199	$9,005,732
25% admission for septicaemia	370	$2,487,645	$3,245,757	$4,223,927
2% liver transplant	30	$3,474,255	$4,533,037	$5,899,153
Severe cirrhosis and HCC- 1 admission	2,634	$2,206,015 - $45,590,984	$2,878,300 - $59,484,869	$3,745,730 - $77,411,760
14% with HCC	369	$4,148,312	$5,412,513	$7,043,676
Terminal care		$94,925,510	$123,854,127	$161,179,911
Total Costs		**$156,962,151 - $195,090,209**	**$204,796,480 - $254,544,090**	**$266,515,773 - $331,255,767**

Table 55. Costs for medical care for worst case scenario for population 14,700.

In the worst case scenario where the initial population is 14,700 persons total treatment costs for this cohort range from $156,962,151 for the discounted group with only a 1% average rise in the CPI to $341,500,791 undiscounted and with an average rise in the CPI

of 3%. This large increase in cost is due to the higher number of people in the cohort with severe cirrhosis and HCC, requiring much more extensive treatments.

	Number of persons	1% CPI increase	2% CPI increase	3% CPI increase
Undiscounted Costs				
Basic management for HCV	10,254	$5,432,821	$7,088,478	$9,224,724
26% discontinue after 12 weeks	2,666	$4,882,759	$6,370,783	$8,290,739
18% long term response after 6 months	1,846	$6,760,844	$8,821,217	$11,479,657
35% long term response after 12 months	3,589	$24,179,409	$31,548,101	$41,055,718
20% of non-responders develop cirrhosis	1,333	$4,926,429	$6,427,762	$8,364,889
25% admission for septicaemia	333	$2,310,626	$3,014,791	$3,923,355
2% liver transplant	27	$3,227,029	$4,210,468	$5,479,372
Severe cirrhosis and HCC- 1 admission	1,280	$1,105,175 - $22,840,280	$1,441,978 - $29,800,872	$1,876,545 - $38,781,929
14% with HCC	179	$2,078,231	$2,711,574	$3,528,757
Terminal care		$47,556,009	$62,048,737	$80,748,298
Total Costs		**$102,459,332 - $119,311,679**	**$133,683,887 - $155,671,999**	**$173,972,056 - $202,586,701**
3% Discounted Costs				
Basic management for HCV	10,254	$5,269,837	$6,875,823	$8,947,983
26% discontinue after 12 weeks	2,666	$4,736,276	$6,179,660	$8,042,017
18% long term response after 6 months	1,846	$6,558,019	$8,556,580	$11,135,267
35% long term response after 12 months	3,589	$23,454,027	$30,601,658	$39,824,047
20% of non-responders develop cirrhosis	1,333	$4,778,636	$6,234,929	$8,113,942
25% admission for septicaemia	333	$2,241,307	$2,924,347	$3,805,654
2% liver transplant	27	$3,130,218	$4,084,154	$5,314,991
Severe cirrhosis and HCC- 1 admission	1,280	$1,072,020 - $22,155,072	$1,398,718 - $28,906,846	$1,820,249 - $37,618,471
14% with HCC	179	$2,015,884	$2,630,226	$3,422,895
Terminal care		$46,129,329	$60,187,275	$78,325,849
Total Costs		**$99,385,552 - $115,732,328**	**$129,673,371 - $151,001,839**	**$168,752,894 - $196,509,100**

Table 56. Costs for medical care for best case scenario for population 19,600.

The table above shows predicted costs for the best case scenario where the initial population is 19,600 persons. Total treatment costs for this cohort range from $99,385,552 for the discounted group with only a 1% average rise in the CPI to $202,586,701 undiscounted and with an average rise in the CPI of 3%.

	Number of persons	1% CPI increase	2% CPI increase	3% CPI increase
Undiscounted Costs				
Basic management for HCV	15,170	$8,037,439	$10,486,854	$13,647,266
26% discontinue after 12 weeks	3,944	$7,223,406	$9,424,744	$12,265,069
18% long term response after 6 months	2,731	$10,002,146	$13,050,308	$16.983,265
35% long term response after 12 months	5,310	$35,771,565	$46,672,976	$60,738,760
20% of non-responders develop cirrhosis	1,972	$7,288,270	$9,509,376	$12,375,206
25% admission for septicaemia	493	$3,418,392	$4,460,150	$5,804,300
2% liver transplant	39	$4,774,140	$6,229,062	$8,106,308
Severe cirrhosis and HCC- 1 admission	3,513	$3,033,187 - $62,685,863	$3,957,553 - $81,789,426	$5,150,236 - $106,438,216
14% with HCC	492	$5,703,770	$7,441,998	$9,684,785
Terminal care		$130,518,953	$170,294,698	$221,616,227
Total Costs		**$215,771,270 - $268,200,540**	**$281,527,720 - $349,934,848**	**$366,371,424 - $455,394,334**
3% Discounted Costs				
Basic management for HCV	15,170	$7,796,316	$10,172,249	$13,237,8v48
26% discontinue after 12 weeks	3,944	$7,006,704	$9,142,002	$11,897,117
18% long term response after 6 months	2,731	$9,702,082	$12,658,799	$16,473,767
35% long term response after 12 months	5,310	$34,698,418	$45,272,787	$58,916,597
20% of non-responders develop cirrhosis	1,972	$7,069,622	$9,224,095	$12,003,950
25% admission for septicaemia	493	$3,315,841	$4,326,345	$5,630,171
2% liver transplant	39	$4,630,915	$6,042,190	$7,863,119
Severe cirrhosis and HCC- 1 admission	3,513	$2,942,191 - $60,805,288	$3,838,826 - $79,335,743	$4,995,729 - $103,245,070
14% with HCC	492	$5,532,657	$7,218,738	$9,394,242
Terminal care		$126,603,385	$165,185,857	$214,967,740
Total Costs		**$209,298,132 - $260,154,524**	**$273,081,888 - $339,436,803**	**$355,380,281 - $441,732,504**

Table 57. Costs for medical care for worst case scenario for population 19,600.

In the worst case scenario where the initial population is 19,600 persons total treatment costs for this cohort range from $209,298,132 for the discounted group with only a 1% average rise in the CPI to $455,394,334 undiscounted and with an average rise in the CPI of 3%.

CONCLUSION

This study has focused on developing a model to simulate the transmission of hepatitis C among a cohort of intravenous drug users in Perth, Western Australia. In addition, the study has examined the potential costs that may arise in treating these infected persons, both with α-Interferon and other treatments involving hospital admissions.

Using two cohorts sizes representing variations in the intravenous drug using community in Perth, two different probability of infection rates and varying recruitment and migration rates for this population, predicted numbers of persons either with the virus or suffering severe symptoms, are sufficiently large to cause health planners and funding sources concern.

Among the smaller starting cohort of 14,700 IVDU's the best case scenario is one where 7,677 people are infected with the virus and will require normal management and treatment with α-Interferon, and 958 people will be experiencing severe cirrhosis or hepatocellular carcinoma and will require expensive treatment and palliative care measures. Among this group the worst case scenario is one where 11,381 persons are infected with the virus and 2,634 are severely ill.

Examining the larger group (n =19,600), the best scenario resulted in 10,254 persons infected with hepatitis C with 1,280 terminally ill and the worst case involves 15,170 persons infected and 3,513 with severe cirrhosis or hepatocellular carcinoma.

Treatment cost for this cohort are predicted to be large. In the best instance costs would range from $74,396,230 to $86,629,588, while the predicted costs associated with the worst case scenario range from $366,371,424 to $455,394,334.

The mathematical model illustrates the effectiveness of intervention programs, where the number of infected persons decreased when the force of infection was low and the migration rate was increased. This phenomenon was not observed with the higher force of infection, although in both instances the number of severely ill persons, those that require the largest share of the treatment budget, decreased. This has obvious and rather urgent implications for those formulating health policy in regard to intervention programs. Some of these intervention programs are discussed below.

Australia has led the world with its innovative programs of harm minimisation that arose following the advent of HIV/AIDS. Among these programs included needle exchange programs and the availability of Fitpacks. In Western Australia, the only really safe needle program is the Fitpack and these must be bought at the local pharmacy. This process of having to purchase injecting equipment marginalises many IDU's, especially new initiates, leaving them more prone to needle sharing.

Western Australia has a well developed network of medical professionals involved in intervention programs such as Methadone substitution. There is also a program run by a medical practitioner involving rapid detoxification and the implantation of Naltrexone. This program, while receiving government funding it is yet to be accepted as an approved intervention program as it has not undergone stringent clinical trails. The

waiting list for both programs are large, indicating a desire by many IDU's to change their current lifestyles.

Increased funding for these treatment programs would dramatically decrease the number of people in both the susceptible and infectious cohorts, lowering the number who become infected and decreasing the risk of susceptibles sharing injecting equipment with those who are infected. Involvement in a treatment program with readily available medical intervention would also lead to earlier detection of those with the virus, dramatically improving their chances of a sustained response to α-Interferon. This resultant lowering of the number of persons infected with the virus would have a huge impact on future health budgets.

Education programs aimed at young adolescents are also desirable. Brochures that suggest ways to avoid hepatitis C infection are included in the Fitpacks, but many novice IDU's are not confident to purchase this equipment and are more likely to be sharing. While many may be aware of the dangers of HIV/AIDS, fewer are aware of the associated risks of sharing needles and injecting equipment with infection with hepatitis C.

7.1. Limitations and possible improvements to the mathematical model.

No discernable differences were noted between the two different proportions of HCV infection as cited by the 1999 HIV/AIDS, Hepatitis C & Sexually Transmissible Infections in Australia and those given by Crofts (1993). In all simulations the difference

between both sets of data were negligible and in the case of the smaller population cohort at the highest force of infection, almost identical.

Further refinements to the mathematical model might include one that more accurately portrays the growth of the intravenous drug using population in relation to predicted population growths within Western Australia. The current model is dependent only on growth in relation to migration and recruitment rates and these recruitment rates may be better served to also reflect growth in accordance with the growth of the overall population.

Further adjustments to the model could be made via the migration rates. This simulation sets both recruitment and migration rates as equal. Further investigation into these migration rates, from sources such as the number entering and completing treatment programs per year, the average length of time involved in intravenous drug use prior to seeking intervention and the number of fatal overdoses would serve to further refine the migration rate.

It is not inconceivable that with the development of gene technology, a vaccine may be available, at least for the more common types of hepatitis C, within the twenty-year time frame examine in this study. An analysis of the effects on treatment costs compared with vaccination costs for such a vaccine, especially one administered to all young adolescents, would be of interest.

Finally, establishing a model that examined differences among males and females would assist in establishing more precise results. Literature suggests lower infection rates for females than males, most likely due to a more stringent adherence to not sharing needles.

The examination of the treatment cost were based on costings already undertaken by a leading Australian researcher (Sheill et al, 1999). The treatment costs have been applied to the predicted number of persons in each category as suggested by the model, rather than on a hypothetical group of 1000 intravenous drug users. The predicted treatment costs are in line with other published data, most notable Brown and Croft (1998), given that Western Australia has one-tenth of the national population and presumably one-tenth of the intravenous drug using population.

A further addition to this estimation may be to develop a Markov model similar to that developed by Sheill et al, and to apply the predicted number of persons in each category from the simulation and undertake a cost benefits analysis of α-Interferon treatment regimes.

This study has developed a model that will predict future numbers of persons suffering from hepatitis C and the resultant treatment costs that will be incurred. Unless immediate and comprehensive intervention and education programs are instituted, health officials and medical institutions will be faced with an epidemic of persons with hepatitis C and its associated complications. As with all things, money that is wisely invested in prevention today will impact significantly on the quality of life and available resources in future years.

REFERENCES

1999 HIV/AIDS, Hepatitis C & Sexually Transmissible Infections in Australia: Annual Surveillance Report. Edited by National Centre in HIV Epidemiology and Clinical Research.

Aitken, C., Brough, R.& Crofts, N. (1999). Injecting drug use and blood-borne viruses: a comparison of rural and urban Victoria, 1990-95. *Drug and Alcohol -Review.* 18(1):47-52.

Anderson, R.M. and May, R.M. (1991) *Infectious Diseases of Humans - Dynamics and Control.* Oxford University Press, Oxford.

Australian Bureau of Statistics. *Australia Now - A Statistical Profile.* @ http://www.abs.gov.au/websitedbs/c311215...Profile/

Australian Red Cross Blood Service *Estimated risk of transfusion transmitted infection.* @ http://www.arcbs.redcross.org.au/

Bell, J., Batey, R.G., Farrell, G.C., Crewe, E.B., Cunningham, A.L. Byth, K. (1990). Hepatitis C virus in intravenous drug users. *The Medical Journal of Australia.* 153: 274-276.

Bevan, J., Loxley, W., Carruthers, S., (1996) Getting on and getting off in Perth 1994. *Report of the Australian Study of HIV and Injecting Drug Use (ASHIDU). Perth, Western Australia:* Curtin University of Technology, National Centre for Research into the Prevention of Drug Abuse.

Brandt, E.R., Devenish, R.J., Hertzog, P.J., Dudley, F.J., Linnane, A.W. (1994). Detection of interferon-alpha expression by PCR in patients with chronic hepatitis C and hepatitis non-a, non-B. *Journal of Gastroenterology and Hepatology.* Jul.-Aug, 9(4): 373-80.

Brown, K., Crofts, N. (1998). Health care costs of a continuing epidemic of hepatitis C virus infection among injecting drug users. *Australian and New Zealand Journal of Public Health.* 22(3 Suppl): 384-388.

Carruthers, S and Loxley, W. (1994*). Hepatitis C and Young Drug Users. Perth, Western Australia:* Curtin University of Technology, National Centre for Research into the Prevention of Drug Abuse.

Castillo-Chavez, C. (1989) *Mathematical and Statistical Approaches to AIDS Epidemiology.* Lecture Notes in Biomathematics 83. Springer-Verlag. Berlin.

Choo, Q-L., Weiner A.J., Overby, L.R., Kuo, G., Houghton, M. and Bradley, D.W. (1990). Hepatitis C virus: The major causative agent of viral non-A, non-B hepatitis. *British Medical Bulletin.* 46(2): 423-441.

Comiskey C.M. (1993). Modelling AIDS in Ireland. *SIAM News, Society of Industrial and Applied Mathematics, USA.*

Comiskey C.M., Glockner, B. and Roydhouse, R. (1993). Modelling the transmission dynamics of HIV and its progression to AIDS in heterosexuals. *Proceedings of the Xth International Congress on Modelling and Simulation.*

Crofts, N., Hopper, J.L., Bowden, D.S., Breschkin, A.M., Milner, R and Locarnini, S.A. (1993). Hepatitis C virus infection among a cohort of Victorian injecting drug users. *The Medical Journal of Australia.* 159:237-241.

Crofts N. (1993). Response to Hulse et al. *The Medical Journal of Australia.* 159:636-637.

Crofts, N. (1994). Hepatitis C infection among injecting drug users: where do we go from here? (Editorial). *Drug and Alcohol Review.* 13:235-237.v

Crofts, N., Stewart, T., Hearne, P., Ping, X.Y., Breschkin, A.M. and Locarnini, S.A. (1995). Spread of bloodborne viruses among Australian prison entrants. *British Medical Journal.* 310:285-288.

Crofts, N. & Aitken, C.K. (1997) Incidence of blood-borne virus infection and risk behaviours in a cohort of injecting drug users in Victoria, 1990-1995. *The Medical Journal of Australia.* 167:17-20.

Crofts, N., Jolley, D., Kaldor, J., van Beek, I. & Wodak, A. (1997). Epidemiology of hepatitis C virus infection among injecting drug users in Australia. *J. Epidemiol. Community Health.* 51:692-697.

Crofts N., Aitkin KA., & Kaldor JM. (1999). The force of numbers: why hepatitis C is spreading among Australian injecting drug users while HIV is not. *The Medical Journal of Australia.* 170:220-221.

Crofts, N. (2001). Going where the epidemic is – epidemiology and control of hepatitis C among injecting drug users. Australian Family Physician. 30(5): 420-425.

Desland M. & Batey R. (1991) High retention rates within a prospective study of heroin users. *British Journal of Addiction.* 86:859-865

Dolan K., Wodak A., Hall W., and Kaplan E. (1998). A mathematical model of HIV transmission in NSW prisons. *Drug and Alcohol Dependence.* 50:197-202.

Dore, G. J., Freeman, A.J., Law, M. L. and Kaldor, J. M. (2002). Advances in liver disease: Hepatitis C. Is severe liver disease a common outcome for people with chronic hepatitis C? *Journal of Gastroenterology and Hepatology.* 17: 423-430

Dusheiko, G.M. and Roberts, J.A. (1995) Treatment of chronic type B and C hepatitis with Interferon alpha: an economic appraisal. *Hepatology.* 22(6):1863-1873.

English, DR, Holman CDJ., Milne E, et al. *The quantification of drug caused morbidity and mortality in Australia, 1995 edition.* Commonwealth Department of Human Services and Health, Canberra, 1995.

Fairley, C.K., Leslie D.E., Nicholson, S & Gust I.D. (1990). Epidemiology and hepatitis C virus in Victoria. *The Medical Journal of Australia.* 153:271-73.

Frankis, P. (1994) Hepatitis C – the next wave. *Connexions.* 8 – 11

Frankis, P. (1994) Risky business. Injecting drug use and hepatitis C. *Connexions.* 12 – 13

Frankis, P. (1994) Hepatitis explained. *Connexions.* 14 – 15

Freeman, A. J., Law, M. G., Kaldor, J. M. and Dore, G. J. (2003). Predicting progression to cirrhosis in chronic hepatitis C virus infection. *Journal of Viral Hepatitis.* 10: 285-293.

Gabrielli, C., Zannini, A., Corradini, R and Gafa, S. (1994). Spread of hepatitis C virus among sexual partners of HCVAb positive intravenous drug users. *Journal of Infection.* July, 29(1): 17-22.

Gao, Z. (2001). Modelling human immunodeficiency virus and hepatitis C virus epidemics in Australia. Thesis, University of New South Wales.

Gerald, C.F. and Wheatley, P.O. (1994). *Applied Numerical Analysis. 5th Edition.* Reading Massachusetts: Addison-Wesley.

Grifiths-Jones, A. (1994) Hepatitis Revisited. *Nursing Times.* Nov. 90(46): 58-62.

Hall, W. (1997) *Centre Lines* 29:2

Hall, W. (1999) The 1998 James Rankin Oration. Reducing the toll of opioid overdose deaths in Australia. *Drug and Alcohol Review.* 18(2):213-220

Hando, J., Howard, J. & Zibert, E. (1997). Risky drug practices and treatment needs of youth detained in New South Wales Juvenile Justice Centres. *Drug and Alcohol Review.* 16(2):137-145.

Hantz, O., Turin, F., Trepo, C. (1993). Therapy for Hepatitis, with emphasis on the role of Interferon's. *Current Opinion in Infectious Diseases.* Dec, 6(6): 778-83, 856-7.

Hulse, G.K., Moore, L.L. &Lambert T.J. (1993) Injecting drug use: a continuing and major vehicle for transmission of infection. *The Medical Journal of Australia.* 159:635-636.

Iwarson, S. (1994). The natural course of chronic hepatitis C. *FEMS Microbiology Review.* 14(3): 201-204.

Kaldor, J.M., Archer, G.T., Buring, M.L., Ismay, S.L. Kendrick, K.G., Lien, A.S.M., Purusothaman, K., Tulloch, R., Bolton, W.V. and Wylie, B.R. (1992). Risk factors for hepatitis C virus infection in blood donors: a case-control study. *The Medical Journal of Australia.* 157:227-230.

Kane, A., Lloyd, J., Zaffran, M., Simonsen, L. and Kane, M. (1999). Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. *Bulletin of the World Health Organisation.* 77(10): 801-807.

Kermack, W.O. & McKendrick, A.G. (1927). *Contributions to the mathematical theory of epidemics.* Proc.Roy. Soc.

Kew, Michael C. (1994). Hepatitis C virus and hepatocellular carcinoma. *FEMS Microbiology Review*. 14(3): 211-220.

Kim, W.R., Gross, J.B. Jr., Poterucha, J.J., Locke, G.R. 3rd., Dickson, E.R. (2001). Outcomes of hospital care of liver disease associated with hepatitis C in the United States. *Hepatology*. Jan, 33(1): 201-206

Koff, R.S. and Seeff, L.B. (1995) Economic modelling of treatment in chronic hepatitis B and chronic hepatitis C: promises and limitations. *Hepatology*. 22(6):1880-1882.

Larson A and Bammer G. (1996). Why? Who? How? Estimating numbers of illicit drug users: lessons from a case study from the Australian Capital Territory. *Australian and New Zealand Journal of Public Health*. 20(5): 493 – 499.

Laslett, A & Rumbold G. (1998). The epidemiology of Australian drug use. *In Drug use in Australia*. Ed Hamilton, M, Kellehear A & Rumbold G. Oxford University Press, Oxford.

Law, M. G. (1999). Modelling the hepatitis C virus epidemic in Australia. *Journal of Gastroenterology and Hepatology*. 14: 1100-1107.

Law, M.G., Dore, G.J., Bath, N., Thompson, S., Crofts, N., Dolan, K., Giles, W., Gow, P., Kaldor, J., Loveday, S., Powell, E., Spencer, J. and Wodak, A. (2003). Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001. *International Journal of Epidemiology*. 32: 717-724.

Lenton, S. & Tan-Quigley, A. (1997) *The Fitpack Study: A survey of 'hidden' drug injectors with minimal drug treatment experience. Perth, Western Australia:* National Centre for Research into the Prevention of Drug Abuse, Curtin University of Technology.

Lin, R., Liddle, C., Byth, K and Farrell, G.C. (1996). Virus and host factors are both important determinants of response to interferon treatment among patients with chronic heaptitis C. *Journal of Viral Hepatitis.* 3:85-96.

Lisanti, P. & Talotta, D. (1994). An overview of Viral Hepatitis: A through E. *AORN Journa.* May, 59(5): 997-8, 1000-5.

Loxley, W & Davidson, R. (1991). Why do injecting drug users take risks? Barriers to safer injecting and sexual behaviour in Perth. *National AIDS Bulletin.* October. 32- 38.

Loxley, W. (1997). *At risk and unprotected: Findings from the youth, AIDS and drugs (YAD) study.* National Centre for Research into the Prevention of Drug Abuse, Curtin University of Technology.

Loxley, W.M., Phillips, M., Carruthers, S.J. & Bevan, J.S. (1997) The Australian Study of HIV and Injecting Drug Use. Part 1: Prevalence for HIV, hepatitis B and hepatitis C among injecting drug users in four Australian cities. *Drug and Alcohol Review.* 16(3):207-214.

Lynskey, M.T., and Hall, W. (1998). Cohort trends in age of initiation to heroin use. *Drug and Alcohol Review.* 17:289-297.

Maddrey, W.C. (1994). Chronic viral hepatitis: diagnosis and management. *Hospital Practice.* Feb., 29(2): 117-20, 123-4, 126.

Mather, D and Crofts, N. (1999). A computer model of the spread of hepatitis C virus among injecting drug users. *European Journal of Epidemiology.* 15: 5-10

M^{c}Omish, F., Yap, P.L., Dow, B.C., Follett, E.A.C., Seed, C., Keller, A.J., Cobain, T.J., Krusius, T., Simmonds, P. (1994). Geographical distribution of hepatitis C Virus genotype in blood donors: An international collaborative study. *Journal of Clinical Microbiology.* 32(4): 884-892.

Murray, J. M., Law, M. G., Gao, Z. and Kaldor, J. M. (2003). The impact of behavioural changes on the prevalence of human immunodeficiency virus and hepatitis C among injecting drug users. *International Journal of Epidemiology.* 32: 708-714.

Nakajiri, K., Ichikara, K., Ohmoto, K., Hirokawa, M., and Matsuda, N. (1993). Analysis of discordant test results among five second-generation assays for anti-hepatitis C virus antibodies also tested by polymerase chain reaction-RNA assay and other laboratory and clinical tests for hepatitis. *Journal of Clinical Microbiology.* 31(11): 2974-2980.

Nakashima, K., Kashiwagi, S., Hayashi, J., Noguchi, A., Hirata, M., Kajiyama, W., Urabe, K., Minami, K., and Maeda, Y. (1992). Sexual transmission of hepatitis C virus among female prostitutes and patients with sexually transmitted diseases in Fukuosha, Kyushu, Japan. *Am. J. Epidemiol.* 136:1132-7.

Phipps, W.J., Long, B.C. & Woods, N.F. (1979) *Medical-surgical nursing: Concepts and clinical practice.* St. Louis: The C.V. Mosby Company.

Price, Sylvia A. & Wilson, Lorraine M. (1982). *Pathophysiology: Clinical concepts of disease processes.* USA: McGraw-Hill.

Ross, M.W., Stowe, A., Wodak, A. & Gold, J. (1993). Changes in equipment sharing in injecting drug users in Sydney 1989 –1990. *Drug and Alcohol Review.* 12:277-281.

Sato, B et al. (1994). Heterosexual transmission of hepatitis C virus and the possible role of co-existent human immunodeficiency virus infection in the index case. A multi-centre study of 423 pairings. *Journal of Internal Medicine.* Nov., 236(5): 515-9.

Schiff, E.R.. (1993). The patient with chronic hepatitis C... including commentary by Greenburger, N.J. *Hospital Practice.* Aug., 28(8): 25-33.

Shiell, A., Briggs, A., Farrell, G.C. (1994) The cost effectiveness of alpha interferon in the treatment of chronic active hepatitis C. *Medical Journal of Australia.* March 7, 160(5): 268-72.

Sheill, A.., Brown, S., Farrell, G.C. (1999). Hepatitis C: an economic evaluation of extended treatment with interferon. *The Medical Journal of Australia.* 171:189-193.

Steven, I.D., Gills, J.S., & Hall, R. (1994). Hepatitis C. *Australian Family Physician.* Sep., 23(9): 1747-8.

The Royal Australian College of General Practitioners. *National hepatitis C management guide for GP's.* @ http://www.racgp.org.au/open/projects/hepc/support5.htm

Van Beek, I., Buckley, R., Stewart, M., MacDonald, M., Kaldor, J. (1994) Risk factors for hepatitis C virus infection among injecting drug users in Sydney. *Genitourin. Med.* Oct., 70: 321-324.

Waddell, R.G. (1994). Hepatitis C and the history of injecting drug use in South Australia. *The Medical Journal of Australia.* 161: 286.

Watson, K. J. R. (2000). Preventing hepatitis C virus transmission in Australians who inject drugs. *Medical Journal of Australia.* 172: 55-56.

Wodak, A. (1997) The 1996 James Rankin Oration: Injecting nation: achieving control of hepatitis C in Australia. *Drug and Alcohol Review.* 16(3):275-284

Wong, J.B., Bennett, W.G., Koff, R.S., Pauker, S.G. (1999). Pretreatment evaluation of chronic hepatitis C: risks, benefits and costs. *JAMA.* Jun, 281(22): 2083-2084

Wong, J.B. (1999). Cost effectiveness of treatments for chronic hepatitis C. *American Journal of Medicine.* Dec, 107(6B): 74S-78S.

Yano, M., Kumada, H., Kage, M., Ikeda, K., Shimamatsu, K., Inoue, O., Hashimoto, E., Lefkowitch, J.H., Ludwig, J., Okuda, K. (1996) The long-term pathological evolution of chronic hepatitis C. *Hepatology.* Jun., 23(6): 1334-40.

Zein, N.N., and Rakela, J. (1995). Interferon therapy in Hepatitis C. *Seminars in Gastrointestinal Disease.* Jan., 6(1): 46-53.