Modelling the hepatitis C virus disease burden among injecting drug users in Scotland

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A thesis submitted for the degree of Doctor of Philosophy with the

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October 2004

This thesis is dedicated to my parents

Summary

To plan a public health response to the hepatitis C virus (HCV) epidemic in Scotland, in terms of treatment needs and preventive measures, quantitative estimates of the current and future burden of HCV disease are required. The overwhelming majority of HCV infections in Scotland have been associated with injecting drug users (IDUs); therefore, the work described in this thesis focussed on this risk group. A forward projection model was used to estimate the numbers of, both current and former, IDUs who acquired HCV infection and progressed to mild, moderate and severe HCV disease in Glasgow and Scotland between 1960 and 2030. The model was developed initially for Glasgow because more epidemiological information exists for this region, than elsewhere in Scotland, to calibrate model outcomes with local data relating to HCV and its consequences. Insights gained from the model fitting process in Glasgow were then used to extend the model to the rest of Scotland.

First, the incidence and cessation of injecting drug use in Glasgow during 1960-2000 were derived through the use of a modified Delphi approach. Instead of the usual iterative process to refine experts' estimates, the elicitation of IDU incidence and cessation provided an opportunity to combine these data and examine coherence with capture-recapture IDU prevalence estimates. Coherent estimates indicated that incidence (median: 28 to 49) and cessation (1 to 2%) remained low and stable during 1960-1975, rose steeply between 1975-1985 (incidence from 49 to 1,335; cessation from 2% to 6%), and by 2000 there had been a decline in incidence (1,195) but a further rise in cessation (15%).

Secondly, stochastic simulation was used to model the transmission of HCV among current IDUs in Glasgow, according to their injecting risk behaviours, and

estimate the past incidence of HCV infection. The model that considered higher infectivity during acute viraemia following infection produced seroprevalences (median: 62-72%) and incidences (18-30 per 100 susceptible injector-years) consistent with observed data during the 1990s. The annual number of new HCV infections among current IDUs in Glasgow was estimated to be low during 1960-1976 (median: 10-60), rise steeply during the early 1980s to peak in 1985 (1,120), stabilise during 1991-1997 (510-610) and rise again during 1998-2000 (710-780). Scenario analyses indicated that potentially as many as 4,500 HCV infections (10^{th} and 90^{th} percentiles: 2,400-7,700) had been prevented in Glasgow during 1988-2000 as a result of harm-reduction measures.

Scenario analyses also permitted the gauging of changes in risk behaviours required to effect appreciable reductions in the incidence of HCV infection. Incidence can be successfully reduced if IDUs who, unavoidably, share needles/syringes confine their borrowing to one person; with this strategy alone, an estimated 5,300 HCV infections (10^{th} and 90^{th} percentiles: 4,100-6,700) could have been averted in Glasgow during 1988-2000. Such insights will inform those responsible for developing new ways to prevent HCV transmission among IDU populations.

Thirdly, linkage of laboratory data on diagnosed HCV antibody positive persons in Scotland to clinical data from hospital and death records provided a unique national epidemiological dataset to estimate the number who had progressed to severe HCV disease. The number of persons with newly developed HCV-related decompensated cirrhosis in Scotland was estimated to have increased from 230 (95% CI 220-250) in 1996-1998 to 300 (280-320) in 1999-2001, highlighting HCV as a growing burden on healthcare resources. Alcohol was a prominent factor among persons who had died (78% of 134) or were hospitalised (72% of 442) with HCV-

related decompensated cirrhosis during 1996-2001 in Scotland. The younger age of decompensated patients presenting to hospital with both HCV and alcohol (78% of 320 were aged <50 years old) suggests that the combined effect of these two factors accelerates liver disease progression more than if only one of these factors were present (HCV: 48% of 122; alcohol: 33% of 8,465).

Fourthly, a meta-analysis was carried out to explore the relationship between HCV chronic liver disease and the consumption of alcohol. The pooled relative risk of cirrhosis associated with heavy alcohol intake (defined in the range of at least 210 to 560g per week) was 2.33 (95% CI 1.67-3.26) by the random effects model. Studies investigating the risk of HCV-related cirrhosis include patients undergoing liver biopsy and therefore could under-represent heavy alcohol users; such selectivity may have under-estimated the regression effect of alcohol.

Finally, the HCV projection model was designed to synthesize information on the incidence and cessation of injecting drug use, the incidence of HCV infection among current IDUs, the rate of HCV disease progression (including the influence of alcohol and other host factors), and the annual number of IDUs developing HCV-related decompensated cirrhosis. A total of 17,400 (95% CI 14,300-22,200) and 42,900 (32,400-60,600) persons, who had ever injected drugs, were estimated to be living with HCV antibodies by the end of 2003 in Glasgow and Scotland, respectively. This compares with approximately 5,000 (29%) and 13,900 (32%) diagnosed, respectively. Of these HCV-infected IDUs in Glasgow and Scotland, 13,200 (10,800-16,900) and 32,200 (24,300-45,500) were estimated to be living with chronic HCV and therefore at risk of developing cirrhosis. The number of IDUs developing HCV-related decompensated cirrhosis in Scotland is estimated to double between 2000 and 2020. As high as 16% and 27% of Glasgow former IDUs in 2005

aged 30-39 and 40-49 years, respectively, were estimated to have moderate disease (32% and 47% of those chronically infected, respectively), which highlights the potential benefit of targeting HCV testing at former IDUs who belong to these age groups.

The treatment with antiviral therapy of 15,000 former IDUs in Glasgow with moderate HCV disease over the next 26 years (62% of those HCV infected) could potentially prevent between 24% and 86% of severe HCV-related events during 2005-2030 (based on 45% to 100% response and compliance to therapy, respectively). The identification and treatment of a larger proportion of former IDUs with HCV disease, education about the importance of minimal alcohol consumption, and the development of more effective therapies are needed now to help achieve a greater impact on the future morbidity and mortality of this disease.

Declaration

The work in this thesis was undertaken part-time at the Scottish Centre for Infection and Environmental Health (SCIEH) in Glasgow from October 1999 to October 2004, under the joint supervision of Professor David J Goldberg (SCIEH, Glasgow) and Professor Sheila M Bird (MRC Biostatistics Unit, Cambridge).

This thesis comprises original work carried out by the author, with the exception of the electronic record-linkage of the HCV diagnoses database to the hospital, cancer and deaths databases undertaken by the Information and Statistics Division in Edinburgh (described in Section 4.3.4). This thesis contains no material previously published or written by another person, except where referenced. This thesis has not been submitted in part or whole to any other university for any other degree.

Acknowledgements

I would like to express my sincere thanks to my supervisors, Professor David Goldberg and Professor Sheila Bird, who throughout the course of this thesis and beyond it have provided invaluable advice, support and encouragement; I could not have been more fortunate.

I would like to extend special thanks to my colleagues in the BBV and STI team at the Scottish Centre for Infection and Environmental Health for providing an enjoyable and supportive environment to work in (and for the endless supply of chocolate!). Thanks to my friends, especially those who have run many miles and played many games of hockey with me over the past few years, for all their support.

I would also like to acknowledge and thank the following individuals: the twelve experts who participated in the modified Delphi study, described in Chapter 2; Professor Avril Taylor (formerly at SCIEH, Glasgow) and Dr Sheila Cameron (Regional Virus Laboratory, Glasgow) for providing the data from the community-wide surveys of Glasgow injectors, which informed the modelling work described in Chapter 3; Mr James Boyd and the Record Linkage Team at the Information and Statistics Division in Edinburgh for undertaking the record-linkage of the HCV diagnoses database to the hospital, cancer and deaths databases, described in Chapter 4; Dr Wally Gilks and Dr Shaun Seaman (both at the MRC Biostatistics Unit, Cambridge) for their helpful advice.

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Chapter 1: Introduction

1.1 Background to the hepatitis C virus

The hepatitis C virus (HCV) was first discovered in 1989[1] and diagnostic tests to reliably detect infection were subsequently developed[2]. Of those infected with HCV, 60-85% fail to clear the virus[3,4] and consequently are at risk of developing severe liver disease – decompensated cirrhosis and hepatocellular carcinoma (HCC) – over a long and variable incubation period depending on age at infection, gender, alcohol intake and co-infection with HIV[5,6]. There is no vaccine available at present to prevent infection with HCV; however, treatment with pegylated interferon alpha and ribavirin given in combination leads to sustained viral clearance in 50-60% of patients with moderate disease[7,8]. Liver transplantation is the only option to prolong life for patients who have reached severe HCV disease.

HCV is a blood-borne virus that is transmitted primarily through direct percutaneous exposure. Since 1991, screening of blood donors and products for HCV has virtually eradicated transfusion-associated HCV in developed countries[9]. While this infection has been shown to be transmitted vertically from mother to child and through unprotected sexual intercourse[10], HCV in western countries is most commonly transmitted among injecting drug users (IDUs) who share injecting equipment[11]. HCV seroprevalence rates exceeding 50% have been detected among populations of IDUs throughout the world[12].

The World Health Organisation estimated, on the basis of limited country-specific data, that around 170 million people worldwide were chronically infected with HCV in 1997[13]; thus, HCV is more than four times as prevalent as the human immunodeficiency virus (HIV)[14]. In the United States, HCV has become the leading

cause of cirrhosis and liver transplantation[15,16,17]. Scotland is likely to have one of the highest prevalences of HCV in Western Europe because of its high prevalences of (i) IDUs[18,19] and (ii) HCV amongst its IDU population (described below, Table 1.1). Furthermore, HCV has been circulating among IDUs in Scotland since at least the early 1980s[20]; therefore, it is expected that increasing numbers of individuals will begin to present with HCV-related complications over the next 10 to 20 years. Accordingly, it is important that methods to forecast the extent and type of HCV-related disease in Scotland – which the National Health Service, local authorities and non-governmental organisations will need to respond to in future years – are developed.

1.2 Prevalence of HCV infection in Scotland

The prevalence of HCV in Scotland varies considerably depending on the population studied; as in other western countries[10], the highest rates were reported among IDUs and recipients of blood and blood products (described below, Tables 1.1 and 1.2). Of 14,390 persons diagnosed with HCV antibodies in Scotland by the end of June 2002, almost 90% (8,719/9,728) of those for whom at least one risk factor was known had injected drugs, 6% (584/9,728) had received blood or blood products and 4% reported occupational needlestick injuries, tattoos, body piercings or sexual contact[21]. These data, and those described below, clearly illustrate that the current, principal risk factor for HCV infection in Scotland is injecting drug use.

1.2.1 Pregnant women

The unlinked anonymous testing of residual dried blood spots on neonatal metabolic screening cards is regarded as the most cost-effective means of providing minimally

biased estimates of HCV prevalence in a large general population[22]. The overall prevalence of maternal HCV antibodies in Scotland during 2000 was low (0.4%); this rate was higher than that modelled for England/Wales (0.15%)[23] though lower than regional estimates for the rest of Western Europe (1-2%)[24], the United States (2-4%)[25,26,27] and Australia (1.1%)[28]. HCV seroprevalence among Scottish childbearing women is consistent with that expected from injecting drug use as primary route of exposure: highest (i) among 25-29 year olds (0.4-0.57%), (ii) in high deprivation areas (0.92-1.07%), and (iii) in Greater Glasgow (0.83-0.96%) and Grampian (0.38-0.62%) health-board areas. A study of pregnant women in Dundee during 1997 found a significantly higher HCV seroprevalence among those who reported injecting drug use (41% of only 17) than those who had not (0.45% of 3,531) ($p<0.0001$), and also highlighted the increased risk of HCV acquisition among the sexual partners of IDUs (15% of 33)[29].

1.2.2 Children

During June 2002, a pilot study to investigate the feasibility of surveying, anonymously, HCV infection among healthy children by means of an oral fluid specimen was undertaken in the Child Dental Health Department of Glasgow Dental Hospital and School. This study found a HCV seroprevalence of 3% (95% CI 0.4-10.3%) among a small sample of 70 children[30].

1.2.3 Blood donors

The prevalence of HCV antibodies among Scottish blood donors in 1991-1992 was 0.09%[31], a rate which was similar to that detected in parts of England (e.g. London

(0.07%)[32], North West (0.04%)[33]) but lower than that found in the United States (0.36%)[34].

1.2.4 Recipients of blood and blood products

Prior to 1985, most patients with clotting disorders were exposed to HCV through the receipt of contaminated blood products. Evidence of HCV infection was found in all but one of 78 haemophiliacs treated with non-virus inactivated clotting factor concentrates in Edinburgh[35]. In 1985, heat treatment of clotting factor concentrates for haemophiliacs was introduced in Scotland[36].

In 1991, the estimated seroprevalence of HCV in three Glasgow Renal Dialysis Units was 3.9% (19/483)[37]. The number of blood transfusions received and the length of time on dialysis were positively associated with HCV antibody status. HCV antibody testing of all new entrants to dialysis units, and thereafter at six monthly intervals, has since been implemented.

1.2.5 Other patient groups

The HCV antibody prevalence for 16-49 year old males undergoing, or eligible to undergo, surgery was 3.8% (103/2,702)[38]. While the risk of HCV transmission from patient to surgeon is low, the prevalences observed among surgical patients indicate that surgeons working in areas of high injecting drug use prevalence and high HCV prevalence among IDUs will frequently operate on HCV infected patients.

Of 80 patients with histologically confirmed liver cancer presenting to the Royal Infirmary of Edinburgh between 1985 and 1994, 30% were found to be positive for HCV antibodies[39]. This study highlighted that chronic HCV infection could be a major risk factor for the development of HCC in Scotland.

1.2.6 Healthcare workers

The overall prevalence of HCV antibodies among healthcare workers in Glasgow was low (0.28% of 8,412)[40] and comparable with that reported in England (0.21-0.28%)[41,42]. The Glasgow study indicated that the performance of exposure prone procedures does not necessarily result in an increased risk of HCV acquisition by healthcare workers (0.23% of 2,205 currently performing compared to 0.3% of 6,207 not currently performing exposure prone procedures, p=0.6; no significant differences in HCV prevalence were found between these groups stratifying by age). A study of 880 dental healthcare workers in the West of Scotland reported a seroprevalence of 0.1%, from which the authors suggested that HCV was not a significant occupational hazard in the dental setting either[43].

1.2.7 Genitourinary Medicine Clinic Attenders

The HCV seroprevalence among non-injecting heterosexual men and women was 0.8 (32/4,135) and 0.3% (10/3,035), respectively, and 0.6% (4/668) among non-injecting homosexual/bisexual men attending genitourinary medicine clinics in Scotland during 1996-1997[44]. These findings are in keeping with the prevailing view that HCV is not easily transmitted through unprotected sexual intercourse.

1.2.8 Prisoners

HCV antibody prevalence was estimated at 58% and 3.5% among 536 injector and 899 non-injector inmates, respectively, surveyed in five Scottish prisons during 1994-1996[45]. Similarly, 53% and 4.0% of 173 injector and 406 non-injector inmates, respectively, surveyed at Shotts prison during 1999-2000 were estimated to be HCV

antibody positive (personal communication: Dr Jennifer Champion, SCIEH). The prevalence and potential transmissibility of HCV in injector-inmates are therefore both high. For inmates surveyed in 1999-2000 who reported ever having injected drugs, the HCV incidence was 12 (95% CI 5-32) per 100 person-years of incarceration[46].

1.2.9 Injecting drug users

HCV has been circulating among IDUs in Scotland since at least the mid 1970s: 73% of 275 IDUs who had tested hepatitis B surface antibody positive in Glasgow during 1973-1984 were HCV antibody positive (personal communication: Dr. Sheila Cameron, Glasgow Regional Virus Laboratory); similarly, 87% of 126 IDUs who had a hepatitis B surface antibody test in Edinburgh during 1984 were HCV antibody positive[20]. Of almost 2,000 current IDUs recruited during community-wide, multi-site surveys in Glasgow during 1990-1996, the overall estimated HCV seroprevalence was 72%[47]. Seroprevalence rates per survey year ranged from the highest of 79% from 365 IDUs in 1990 to the lowest of 66% from 195 IDUs in 1996. These data suggest that the incidence of HCV among IDUs in Glasgow had decreased during this period.

In the late 1980s and throughout the 1990s, Scotland implemented, and continued to develop, interventions – including the provision of sterile injecting equipment – to reduce needle/syringe sharing and thus the transmission of blood-borne viruses among IDUs[48,49]. To determine if the prevalence of HCV antibodies among IDUs in Scotland had changed in this era of harm reduction, residual sera from IDUs who had undergone a named HIV antibody test during 1989-2000 were tested for HCV antibodies (Table 1.2)[50]; this survey approach revealed significant reductions in HCV seroprevalence among IDUs aged under 25 years from Glasgow and Lothian

between 1990 (Glasgow 91%; Lothian 69%) and 1995 (59%; 31%) and 1997 (43%; 13%), suggesting that there had been a steady, continual decrease in the incidence of HCV. However, no further significant reductions in HCV seroprevalence were found among this group during the late 1990s (Glasgow 1997 and 1999-2000: 43% and 41%, respectively; Lothian 1997 and 1999: 13% and 17%, respectively; Table 1.2). The most recent findings highlight that existing harm reduction measures, acknowledged as having helped to reduce the spread of HCV, are not sufficient to bring this epidemic under control. The high seroprevalence of HCV (58% of 466) detected among recently initiated IDUs (i.e. average of 2-3 years' injecting career) surveyed in Glasgow during 2001-2002 suggests that the incidence of HCV might be on the increase (personal communication: Dr. Sarah Wadd, SCIEH); such a trend would be consistent with the observed increase in injecting risk behaviours in 1999 compared to previous years 1991-1994[51].

1.3 Public health relevance of projecting the future HCV-related disease burden

Most of those infected with HCV in Scotland, as in many other developed countries, acquired their infection at a young adult age and during the past thirty years through the sharing of contaminated injecting equipment. Given that HCV progresses slowly, particularly among young adults, and does not result in major morbidity and mortality for many years, then Scotland has not yet experienced the full consequences of this epidemic. As the large pool of currently infected patients ages and their disease has time to progress, more patients will develop complications of liver disease and the burden on the healthcare system will increase as a result.

As at the end of June 2002, a total of 14,390 persons had been diagnosed with HCV in Scotland[21], of whom only 1,500-3,000 were likely to have been in active

follow-up with specialist care services and even fewer (1,000-1,500) had received antiviral treatment[52]. Plausibly, a major factor contributing to the low uptake of antiviral therapy was the ineligibility of many cases due to their current injecting status at the time of diagnosis. Based on a study among pregnant women[53], it was estimated that 70-80% of HCV infected women (of childbearing age) in Scotland during 2000 were undiagnosed; accordingly such individuals were making few demands on HCV-related healthcare services. Overall, the current burden placed on the healthcare system in Scotland by HCV is relatively small when placed in the context of the large reservoir of infected persons. That said, waiting times for new patient appointments to see a specialist for evaluation of HCV disease in Scotland range, depending on region, between several months and several years. Strategies to diagnose, monitor and successfully treat chronic HCV infection need to be designed, evaluated, funded and implemented before large numbers of individuals start to develop severe liver disease, which is unresponsive to antiviral therapy. Treatment of severe liver disease is limited by the shortage of cadaveric donor livers for transplantation[54].

Patients with chronic hepatitis use healthcare resources in obvious and direct ways, such as clinic visits, diagnostic tests, counselling, drug therapy, hospitalisation for the management of liver failure and HCC, and liver transplantation. Care of patients with HCV is provided by a wide range of professionals from many different disciplines including health promotion, primary care, drug addiction services, voluntary sector, social work services, prisons, blood transfusion service, genito-urinary medicine, obstetrics, neonatology, virology, gastroenterology, hepatology, infectious diseases, haematology, public health and occupational health. The high cost

of managing patients with HCV enforces the need for a systematic approach to this condition so that resources are used most effectively.

Services provided for prevention, detection and management of chronic HCV in Scotland have so far been guided by a national needs assessment[52] and regional strategies[55]. Projections (with uncertainty limits) of moderate and severe HCV-related disease will further inform the planning, and subsequent costing, of healthcare provision for HCV-infected patients. By producing projections with, and without, implementation of a range of treatment and prevention interventions, the effectiveness (and cost) of these strategies for reducing, or delaying, the incidence of severe HCV-related disease can be assessed and compared with similar data on competing treatment and prevention regimes associated with other conditions. These data will thus ultimately inform the Scottish Executive Health Department as to the level of priority to give HCV infection in the nation's healthcare budget.

1.4 The role of modelling in the study of infectious diseases

Mathematical and statistical models have played a significant role in shaping our understanding of the epidemiology of infectious diseases. Primarily, infectious disease models have been used to (i) quantify the relationships between characteristics of a specific disease, the contact patterns in the population which cause transmission and the resulting incidence and prevalence of the disease, (ii) estimate the potential impact of proposed interventions on the incidence and prevalence of the disease, and (iii) forecast future trends in disease burden.

Transmission models have helped to determine the key factors influencing the spread of HIV and other sexually transmitted diseases[56], such as the role of specific groups of individuals with high-risk injecting and sexual behaviours[57]. The natural

history of HIV infection has largely been informed from cohort studies, but the effect of possibly important biological parameters, which could not be easily studied empirically, has been postulated from modelling. For example, Longini et al.[58] argued based on modelling results that infectiousness is very high in the first acute phase of HIV infection, very low during the long asymptomatic phase and high again when the first symptoms of AIDS become manifest. The effect of this phenomenon was similarly explored in modelling work, presented in Chapter 3, undertaken to assess the transmission of HCV among IDUs in Glasgow.

Transmission models have also been used to evaluate the effectiveness of behavioural and medical interventions on the spread of infectious diseases[59]. Kaplan[60] modelled the spread of HIV among IDUs via shared needles/syringes in shooting galleries and illustrated that the provision of sterile injecting equipment to this population by needle exchange programmes could significantly reduce the risk of new infections. Mathematical models of the transmission dynamics of the hepatitis B virus have provided the framework to assess the costs and benefits of different vaccination strategies[61]. In recent years, models have been developed to help explore the impact of control measures on the spread of hospital-acquired infections[62], smallpox from a bioterrorism attack[63], and the foot and mouth epidemic[64]. Chapter 3 presents the findings of a HCV transmission model among IDUs in Glasgow, which investigated the changes in injecting risk behaviours required to effect appreciable reductions in the incidence and prevalence of HCV infection in this population. Furthermore, Chapter 6 outlines the impact of different antiviral treatment strategies on the future incidence of severe HCV-related disease from modelling work undertaken among IDUs in Glasgow.

Statistical modelling techniques have been developed to forecast the future course of infectious disease epidemics. The back-calculation method has been most widely used in projections of acquired immune deficiency syndrome (AIDS)[65,66] and, more recently, variant Creutzfeldt-Jakob disease[67]. This approach combines available data on the number of reported cases of disease (e.g. AIDS), after adjustment for reporting delays, with a mathematical representation of the time course between infection and disease diagnosis to back-calculate the number of persons infected in the past and then project forward to obtain predictions of the future incidence of disease. The application of the back-calculation technique, and other modelling approaches, to generate projections of HCV-related severe sequelae is discussed in Section 1.5 below.

1.5 Previous modelling approaches to projecting the future HCV-related disease burden

Markov models have been developed to determine the cost-effectiveness of treating chronic HCV infection with antiviral therapy[68,69,70,71,72,73], the cost-effectiveness of pre-treatment management strategies[74,75], and the future healthcare costs of not treating HCV infection among IDUs[76,77]. The prospect of an alarming rise in HCV-related sequelae over the next 10 to 20 years is generally recognized, and thus recently an increasing number of countries – namely France[78,79], Australia[80,81], the United States[82,83,84], Canada[85], Switzerland[86] and Greece[87] – have focussed attention on generating projections of their HCV epidemics. Few of these have however attempted to validate their projections by comparing model outcomes to past epidemiological trends relating to HCV and its consequences[83].

Precise quantification of the future HCV-associated morbidity and mortality burden requires knowledge of both the past incidence of HCV infection and the natural history of the disease. Reliable data on the progression of HCV infection are beginning to accumulate as the length of follow-up in cohorts of chronically infected cases increases. However, determining the time of HCV acquisition for all currently infected subjects is problematic because most acute infections are asymptomatic, clinical disease is greatly under-reported, and a diagnostic test for HCV has been available only since 1991 yet epidemics have been established for many decades.

Table 1.3 outlines the approaches used previously to model the future HCV-related disease burden in other countries, with emphasis on: (i) estimation of the past incidence of HCV infection, (ii) account for mortality from causes unrelated to HCV, (iii) assumptions used to model the progression of HCV disease, and (iv) data used to validate model results.

1.5.1 Estimation of the past incidence of HCV infection

In previous HCV projection models, the past incidence of HCV infection has been generated through different approaches: (1) back-calculation of HCV-related HCC deaths, (2) estimation of the past pattern of injecting drug use and HCV incidence among IDUs, (3) adjustment of surveillance data on acute HCV, and (4) calibration of HCV seroprevalence and HCC mortality data. Rather than gauge the past incidence of HCV infection, a fifth approach estimated the number of persons currently infected with HCV by stage of disease. These five approaches are described below.

1.5.1.1 Back-calculation from HCV-related HCC deaths

Deuffic et al.[78] employed the back-calculation technique with French statistics on HCV-related HCC deaths during 1979-1995 (and 1979-1998 in an updated analysis[79]), in combination with data on the age distribution at infection and a general model of the natural history of HCV disease, to estimate the annual incidence of HCV through an optimisation process which essentially minimized the difference between modelled and observed HCC deaths data.

Implementation of the back-calculation model relies on the proportion of HCC deaths attributed to HCV being known and also on the consistency and completeness of death statistics over the entire time-period. Even if this information, and other key data described above, were available, the slow progression of the virus is likely to hinder the wider application of this approach to other countries. Many decades can elapse before decompensated cirrhosis or HCC develops after primary HCV infection. France's HCV epidemic dated back to the 1940s, with 12,000 new infections estimated during its mid-epidemic year in 1955. As a result, France witnessed between 1,000 and 1,700 HCV-related HCC deaths per annum during the 1990s[78]. Therefore, a country's HCV epidemic would need to have been established well before 1970 to culminate in substantial numbers of HCC deaths during the 1990s.

1.5.1.2 Estimation of the past pattern of injecting drug use and HCV incidence among IDUs

The approach adopted by Law et al. in 1999[80] and 2003[81] on behalf of the Hepatitis C Virus Projections Working Group in Australia focussed on the IDU population and applied the following strategy: (i) first, the number of people injecting drugs in Australia over the last three decades was estimated; (ii) based on this pattern of

injecting drug use and estimates of HCV incidence among IDUs derived from cohort studies, HCV incidence as a result of injecting drug use was estimated; (iii) these estimates of HCV incidence due to injecting drug use were then adjusted in accordance with the available epidemiological data to allow for HCV infections through other transmission routes, including receipt of blood and blood products.

Lack of data on the prevalent number of IDUs in Australia at the time of the first HCV projection report meant that the Delphi technique was used to reach consensus estimates[80]. The second Australian projection report was able to refine these estimates based on data obtained through modelling of overdose deaths, methadone maintenance episodes and heroin arrests[81]. Law et al. acknowledged that the incidence of HCV infection estimated through this approach was particularly sensitive to assumptions regarding the numbers of IDUs and HCV incidence rates among IDUs and emphasised the need to corroborate model results with available epidemiological data.

1.5.1.3 Adjustment of surveillance data on acute HCV

The most recent model developed for the United States by Davis et al.[84] estimated the annual incidence of HCV infection during 1982-1995 according to the annual number of acute HCV infections reported to the Centre for Disease Control and Prevention (CDC) sentinel surveillance system, with adjustment for significant underreporting and the recognition of only symptomatic acute infection[88,89]. The annual incidence of infection for the years 1950 to 1981 was assumed the same as for 1982, which most likely overestimated infections during these years.

1.5.1.4 Calibration of HCV seroprevalence and HCC mortality data

Another group in the United States applied a model fitting approach to estimate the past incidence of HCV infection using information on HCV seroprevalence and HCC mortality simultaneously. A comprehensive and complex model was designed to follow the entire population from birth to death, with acquisition of HCV assumed to occur through three major routes: mother-to-child transmission, transfusion-associated infection and community infection, including injection drug use and sexual transmission. Numerous assumptions were explored to depict the HCV incidence patterns through these three risk categories. A review of the literature was conducted to define plausible ranges around model parameters (on acquisition of infection, probability of persistence and risk of progression to end-stage liver disease), and multiple simulations of the model were undertaken using sampled values from these ranges. Model predictions produced by each set of sampled values were compared with data on HCV seroprevalence and HCC mortality and a range of HCV incidence curves, which produced consistent results, was identified.

1.5.1.5 Estimating the number of persons currently infected with HCV by stage of disease

Wong et al.[82] adopted a different approach for the United States to those described above; using national household survey data, this entailed the estimation of the number of persons infected with HCV by age group in 1991. The authors accepted that this approach had likely underestimated infection because of the household survey's non-representation of prisoners and homeless people. Further, this model did not consider new infections occurring after 1991. Estimates of the prevalent number of HCV infected persons by age were combined with liver biopsy data, from HCV-

infected patients presenting at liver clinics for treatment[90], to determine the number of persons currently infected with HCV by stage of liver disease (i.e. mild hepatitis, moderate hepatitis and cirrhosis). Because these latter patients were involved in treatment trials and subject to selection bias, the authors adjusted the proportion of the simulated population with cirrhosis so that the simulated number of HCV-related deaths matched that estimated from other sources[82].

Sagmeister et al.[86] used a similar approach for Switzerland, which combined (i) HCV antibody prevalence data from blood donors and pregnant women to estimate the number of HCV-infected persons in 1998, with (ii) liver biopsy data[82] to estimate disease stage. The projection models developed for Canada[85] and Greece[87] were based also on the estimated number of persons who were infected with HCV in 1998 and 1991, respectively; no details were provided of the methods used to derive these estimates. The Canadian and Greek models then estimated the dates of HCV acquisition, instead of the current stage of liver disease, for their currently HCV-infected populations; this was achieved by assignment of infected cases to either age or transmission groups and assignment of duration of HCV infection intervals to each infected case on the basis of their age or transmission group, according to data from various sources but mainly from patients enrolled in treatment studies. The Greek model acknowledged the potential under-representation of HCV-infected IDUs in the treatment studies and thus performed sensitivity analyses assuming a much higher proportion of this risk group[87].

1.5.2 Accounting for mortality from causes unrelated to HCV

Seven of the ten previous projection models applied general population, some age and gender specific, rates of mortality to account for the death of simulated subjects from

causes unrelated to HCV (Table 1.3). The remaining three applications, more appropriately, have taken account of the additional non-HCV-related mortality risk for individuals who acquire HCV infection compared to the general population: the most recent Australian model assumed a 1% annual mortality due to injecting drug use[81]; Wong et al. explored the effect of an excess mortality risk for persons who acquired their HCV through injection drug use (i.e. relative risk of 14, 10 and 4 for those aged <21, 21-30, >30 years, respectively, compared to the general population) and blood transfusion (i.e. additive risk of 0.15 per year)[82]; and Salomon et al. assumed a 2 to 5 times higher risk of death among HCV-infected persons compared to the general population[83].

1.5.3 Assumptions used to model the progression of HCV disease

Several HCV projection models, undertaken in the United States[82,84], Canada[85] and Switzerland[86], based their assumptions on the natural history of HCV on an early Markov model developed by Bennett et al. to determine the cost-effectiveness of treating chronic HCV infection with antiviral therapy[68]. In this model, 80% of newly HCV-infected persons developed chronic infection: this percentage has since been shown to vary between 60 and 90%[3,4], although only the model proposed by Salomon et al.[83] accommodated this range.

Bennett et al. estimated that approximately 30% of HCV chronically infected persons would progress to cirrhosis within 20 years of infection, according to three cohort studies involving only 126 patients[91,92]. The disease progression parameters in this model have remained largely unchallenged, and have been applied elsewhere[82,84,85,86], despite an improved understanding of the natural history of HCV[93]. In a systematic review of 57 natural history studies, estimates of progression

to cirrhosis at 20 years among HCV chronically infected persons varied considerably depending on the methodology employed: 24% (95% CI 11-37%), 22% (18-26%), 7% (4-10%) and 4% (1-7%) among post-transfusion cohorts, liver clinic series, community-based cohorts, and blood donor cohorts, respectively[94]. The community-based studies were generally longitudinal with known time of HCV infection, recruitment was not based on presence of symptomatic or established chronic liver disease, and their combined epidemiological characteristics – mean age of 26 years at infection and injecting drug use reported in 57% – were broadly representative of HCV-infected populations in most western countries. Thus, estimates of disease progression derived from the community-based studies would appear to be the most appropriate for population level HCV natural history models[93] and have been used to produce HCV projections in Australia[81].

Estimates of higher liver disease progression rates may be seen in settings where the prevalence of cofactors for liver disease progression are higher than those observed in the community-based studies included in the systematic review (i.e. mean age at HCV acquisition was 26 years, heavy alcohol intake was reported in 10%, and co-infection with HIV was uncommon)[95]. In particular, settings with a high prevalence of heavy alcohol intake or HIV co-infection would be expected to have higher rates of HCV-related morbidity and mortality, and therefore population level models would need to be adjusted in line with prevalences of these factors and their influence on disease progression. Deuffic et al. found that progression to cirrhosis depended strongly on age at HCV infection and gender: for example, risk of progression to cirrhosis was 300 times higher for men aged 61-70 years than for those aged 21-40 years; and at any age, risk in men was ten times higher than in women[78]. Age and gender adjusted HCV progression rates have frequently been used in HCV

projection models[78,79,83,87], but only Wong et al.[82] explored the influence of heavy alcohol use.

Although some Markov models have overestimated rates of progression to cirrhosis, those from cirrhosis to advanced liver disease complications (i.e. decompensated cirrhosis and HCC) may be more accurate because estimates are less subject to clinic referral bias. The incidences of decompensated cirrhosis and HCC among people with compensated cirrhosis were estimated in the ranges 3-6% and 0.5-4% per year, respectively, although mortality from liver failure and HCC varied considerably in the ranges 14-40% and 30-90% per year, respectively (Table 1.3). Finally, as relatively few HCV chronically infected persons have received antiviral therapy in most western countries (e.g. less than 2.5% in Australia[93]), the impact of current treatment uptake has not been a major feature in HCV projection models.

1.5.4 Data used to validate model results

Several countries have developed models to forecast the future course of their HCV epidemic, but few have validated their predictions by fitting model outcomes to past epidemiological trends relating to HCV and its consequences (Table 1.3). Two of the approaches described above used a model fitting process to derive HCV projections: Deuffic et al. back-calculated from HCV-related HCC deaths data[78,79] and Salomon et al. calibrated data on HCV seroprevalence and HCC mortality[83]. Others have only compared model outcomes with data on the prevalent number of IDUs and HCV-infected persons[84,81]. Salomon et al. suggested that in the development of future projections of HCV epidemics, a minimal requirement might be that models use parameter values that are consistent with past epidemiological data[83].

1.6 Approach to HCV projections for Scotland: aims and overview of methods

As presented in this thesis, a forward estimation and projection approach, similar to that adopted in Australia[80,81], was used to model the past, current and future burden of HCV disease among IDUs in Scotland. The modelling focussed on the IDU population because, as established in Section 1.2, the overwhelming majority of HCV infections and much of the epidemiological data related to HCV in Scotland have been associated with this risk group.

Development of an HCV projection model for Scotland was guided by two fundamental criteria: (a) that the model should accurately reflect both the knowledge and uncertainty about major parameters relating to the epidemiology and natural history of HCV on the basis of the best available local and international data, and (b) that modelled outcomes should be consistent with epidemiological data to date describing the population impact of the HCV epidemic in Scotland. A limitation of the majority of previous modelling efforts, as discussed above in Section 1.4.4, was the absence of the latter constraint in checking the validity of model predictions.

The overall aim is to estimate the number of, both current and former, IDUs who have acquired HCV infection and will progress to mild, moderate and severe HCV disease now and in the future. Figure 1.1 outlines the division by chapters of the data which were used (a) as input parameters to and (b) to check the validity of the HCV projection model. The strategy was to capture the essential features of the HCV epidemic among IDUs initially in Glasgow, because more epidemiological data exist for this region than elsewhere in Scotland, and calibrate model outcomes with available data relating to HCV and its consequences. Insights gained from the model fitting process in Glasgow on the epidemiology and natural history of HCV were used to improve the basis for extending the model to the rest of Scotland. It was important

to distinguish between current and former IDUs not only for purposes of modelling the HCV epidemic, but also to help establish the number of HCV chronically infected IDUs eligible for antiviral therapy; current injecting drug use, generally, is a contraindication to antiviral therapy because of poor compliance and the risk of re-infection with HCV.

The HCV progression model was designed to incorporate both the knowledge and uncertainty about major parameters relating to (i) the incidence and cessation of injecting drug use and mortality from causes unrelated to HCV, (ii) the incidence of HCV infection among current IDUs, and (iii) the rate of HCV disease progression, including the influence of host factors (Figure 1.1(a)). First, the incidence and cessation of injecting drug use in Glasgow were derived through the use of a modified Delphi approach, which combined expert opinion with capture-recapture IDU prevalence estimates, as described in Chapter 2. Mortality from causes unrelated to HCV among current and former IDUs was based on estimates from the literature, as detailed in Chapter 6. Secondly, stochastic simulation was developed to model the transmission of HCV among current IDUs in Glasgow, according to the injecting risk behaviours and the characteristics (i.e. transmissibility and chronicity) of the virus, and to estimate the incidence of HCV infection, as described in Chapter 3. The transmission model detailed in Chapter 3 was also used to examine the impact of changes in injecting risk behaviours on the incidence of HCV infection. For the third component of the projection model, the worldwide literature was reviewed to inform the rate of HCV disease progression, as detailed in Chapter 6. A meta-analysis was performed to quantify the effect of heavy alcohol use on progression to cirrhosis in persons with chronic HCV, as described in Chapter 5.

Modelled outcomes were fitted to epidemiological data on the prevalent number of current IDUs (based on published capture-recapture estimates described in Chapter 2), the prevalence of HCV infection among current IDUs (based on survey data described in Chapter 3), and the number of IDUs developing HCV-related decompensated cirrhosis each year (Figure 1.1 (b)). The latter data on the occurrence of HCV-related liver failure were obtained through record-linkage of Scotland's national surveillance system of all persons diagnosed HCV antibody positive with other national computerised databases on hospital discharges and deaths, as described in Chapter 4. Chapter 6 then synthesizes the data gathered in previous chapters to develop a comprehensive model to estimate the number of current and former IDUs who had acquired HCV infection and progressed to mild, moderate and severe HCV disease in Glasgow and Scotland, 1960-2030. Finally, this projection model was used to explore the impact of different antiviral treatment strategies on the future incidence of severe HCV-related disease.

Table 1.1: Estimates of HCV seroprevalence among different populations surveyed in Scotland to the end of 2002.

Population	Region	Method	Survey year	N	HCV seroprevalence % (95% CI)	First author (reference)
Pregnant women						
Antenatal clinic attenders	Glasgow	VAT of serum specimens	1992	297	1.0 (0.3 - 3.2)	MacLean ([96])
Non-IDU & sexual partner of non-IDU	Dundee	UAT of serum specimens taken for either a routine named or anonymous HIV test	1997	3,498	0.3 (0.2 - 0.6)	Goldberg ([29])
Non-IDU & sexual partner of IDU				33	15.0 (5.1 -31.9)	
IDU				17	41.0 (18.4 -67.1)	
All childbearing women	Scotland	UAT of dried blood spot specimens from routine neonatal screening	2000	30,259	0.4 (0.3 - 0.5)	Hutchinson ([53])
Children	Glasgow	VAT of saliva specimens‡, recruitment from a Dental Hospital	2002	70	3.0 (0.4 -10.3)	Chatzipantazi ([30])
Blood donors	Scotland	Routine screening of blood donations	1991-1992	180,658	0.09 (0.08- 0.1)	Crawford ([31])
Haemophiliacs	Edinburgh	UAT of stored serum samples	1980s	78	98.7 (92.1 -99.9)	Watson ([35])
Dialysis patients (adults)	Glasgow	UAT of serum specimens taken for a hepatitis B surface antibody test	1991	483	3.9 (2.2 - 5.7)	McIntyre ([37])
Surgical patients (men aged 16-49 years)	Glasgow	UAT of serum specimens taken for routine urea and electrolyte testing	1996-1997	2,702	3.8 (3.1 - 4.5)	Thorburn ([38])
Liver cancer patients	Edinburgh	Retrospective testing of stored serum specimens	1985-1994	80	30.0 (20.0 -40.0)	Haydon ([39])
Healthcare workers						
Staff performing exposure prone procedures	Glasgow	UAT of serum specimens taken for a hepatitis B surface antibody test	1993-1996	2,205	0.2 (0.1 - 0.5)	Thorburn ([40])
Other medical staff				6,207	0.3 (0.2 - 0.4)	
Dental staff	West Scotland	VAT of serum specimens	1998-2000	880	0.1 (0.0 - 0.6)	Roy ([43])
Genitourinary Medicine Clinic Attenders						
Non-IDU heterosexual males	Scotland	UAT of serum specimens taken for syphilis serology (in Aberdeen, Edinburgh and Glasgow)	1996-1997	4,135	0.8 (0.5 - 1.1)	Goldberg ([44])
Non-IDU heterosexual females				3,035	0.3 (0.2 - 0.6)	
Non-IDU homosexual/bisexual males				668	0.6 (0.2 - 1.5)	
IDU males and females				148	48.6 (40.4 -57.0)	
Prisoners						
Non-IDUs	Scotland	VAT of saliva specimens† at prisons: Aberdeen, Barlinnie, Cornton Vale, Lowmoss and Perth	1994-1996	899	3.5 (2.2 - 4.8)	Gore ([45])
IDUs				536	58.1 (53.2 -63.2)	
Non-IDU males	Scotland	VAT of saliva specimens† at Shotts prison (a maximum-security, long-stay prison)	1999-2000	406	4.0 (2.0 - 6.1)	Champion (PC)
IDU males				173	53.1 (44.4 -61.8)	
Injecting drug users (IDUs)						
IDUs (likely current)	Glasgow	UAT of serum specimens which tested hepatitis B surface antibody positive	1973-1980	73	80.8 (71.8 -89.9)	Cameron (PC)
IDUs (likely current)	Glasgow	UAT of serum specimens which tested hepatitis B surface antibody positive	1984	202	70.8 (64.5 -77.1)	Cameron (PC)
IDUs (likely current)	Glasgow	UAT of serum specimens which tested hepatitis B surface antibody positive	1992-1993	31	74.2 (58.8 -89.6)	Cameron (PC)
Deceased IDUs	Glasgow	Retrospective testing of postmortem serum specimens	1985-1992	48	89.6 (80.9 -98.2)	McCruden ([97])
Current* IDUs	Glasgow	VAT of saliva specimens†; community-wide recruitment approach	1990-1996	1,949	71.8 (69.2 -74.4)	Taylor ([47])
IDUs who had started injecting ≥ 1990	Glasgow	VAT of saliva specimens†; community-wide recruitment approach	1999	436	53.2 (47.6 -58.7)	Taylor (PC)
IDUs who had started injecting ≥ 1996	Glasgow	VAT of saliva specimens‡; community-wide recruitment approach	2001-2002	466	57.5 (52.7 -62.2)	Wadd (PC)
Female street sex workers, who reported IDU	Glasgow	VAT of saliva specimens† at a medical and social work drop-in centre	1999	89	80.6 (69.3 -92.0)	Taylor (PC)
IDUs (likely current)	Edinburgh	UAT of serum specimens taken for a hepatitis B surface antibody test	1983-1984	126	87.3 (81.5 -93.1)	Gore ([20])
IDUs (likely current)	Edinburgh	UAT of serum specimens which tested HIV antibody negative	1980s	33	75.8 (57.4 -88.3)	Watson ([35])
Current and former IDUs	Edinburgh	VNT of serum specimens; search of general practice records	2000	108	67.6 (58.8 -76.4)	Peat ([98])
Current** IDUs	Lanarkshire	VAT of saliva specimens†; community-wide recruitment approach	1997	90	18.4 (9.5 -27.1)	Taylor (PC)
IDUs (mainly current**)	Lanarkshire	VAT of saliva specimens†; community-wide recruitment approach	2000	165	27.1 (19.5 -34.7)	Taylor (PC)
IDUs (likely current)	Inverclyde	UAT of serum specimens which tested hepatitis B surface antibody positive	1996-1999	59	40.7 (28.1 -53.2)	Stevenson ([99])
Current* IDUs	Highland	VAT of saliva specimens†; community-wide recruitment approach	2000-2001	71	54.7 (41.1 -68.4)	Taylor (PC)
IDUs **(see also Table 1.2)**	Scotland	UAT of serum specimens taken for a named HIV test	1999-2000	2,141	44.2 (42.1 -46.3)	Hay ([100])

UAT Unlinked anonymous testing, VAT Voluntary anonymous testing; VNT Voluntary named testing; PC Personal communication; † ‡ Saliva results adjusted here for 85% ad 96% sensitivity of HCV assay, respectively; * Injected previous 2 months; ** Injected previous 6 months.

Table 1.2: Hepatitis C antibody prevalence among injectors in Scotland: unlinked anonymous testing of specimens taken for named HIV testing**.

Region	Age (years)	Year of specimen											
		1990		1993		1995		1996		1997		1999	
		+ve/N	% (95% CI)	+ve/N	% (95% CI)	+ve/N	% (95% CI)	+ve/N	% (95% CI)	+ve/N	% (95% CI)	+ve/N	% (95% CI)
												*1999/2000	
Glasgow*	< 25	140/154	91 (85-95)	-	-	64/108	59 (49-68)	59/97	61 (50-70)	58/136	43 (34-51)	74/181	41 (34-48)
	≥ 25	124/141	88 (81-93)	-	-	221/262	84 (79-88)	190/215	88 (83-92)	259/327	79 (74-83)	281/391	72 (67-76)
	All	264/295	89 (85-93)	-	-	285/370	77 (72-81)	249/312	80 (75-84)	317/463	68 (64-73)	379/611	62 (58-66)
Grampian	< 25	-	-	-	-	-	-	33/120	28 (20-37)	-	-	66/225	29 (24-36)
	≥ 25	-	-	-	-	-	-	49/100	49 (39-59)	-	-	98/209	47 (40-54)
	All	-	-	-	-	-	-	84/223	38 (31-44)	-	-	165/438	38 (33-42)
		*1989/90											
Lothian*	< 25	289/416	69 (65-74)	-	-	33/106	31 (23-41)	19/114	17 (11-25)	15/112	13 (8-21)	22/128	17 (11-25)
	≥ 25	467/585	80 (76-83)	-	-	144/200	72 (65-78)	115/193	60 (52-67)	116/213	54 (48-61)	120/266	45 (39-51)
	All	756/1001	76 (73-78)	-	-	177/306	58 (52-63)	134/307	44 (38-49)	131/327	40 (35-46)	142/394	36 (31-41)
								*1995/96					
Tayside*	< 25	-	-	27/47	57 (42-71)	-	-	47/113	42 (33-51)	15/33	45 (29-63)	18/51	35 (23-50)
	≥ 25	-	-	65/85	76 (66-85)	-	-	199/273	73 (67-78)	89/127	70 (61-78)	66/109	61 (51-70)
	All	-	-	94/134	70 (62-78)	-	-	251/395	64 (59-68)	106/162	65 (58-73)	84/160	53 (44-60)

- Samples not available for testing.

* For injectors in Glasgow 1999/2000, Lothian 1989/90, and Tayside 1995/96, it was not possible to separate the anti-HCV results of specimens into the appropriate calendar years.

** Hutchinson SJ, McIntyre PG, Molyneaux P, et al. Prevalence of hepatitis C among injectors in Scotland 1989-2000: declining trends among young injectors halt in the late 1990s. Epidemiol Infect 2002; 128: 473-477.

Table 1.3: Characteristics of HCV liver disease projection models published up to July 2004.

First author, Country, Year of publication	(i) Estimation of the past incidence of HCV infection	(ii) Account of mortality from causes unrelated to HCV	(iii) Assumptions used to model the progression of HCV disease							(iv) Data used to validate model results	(v) Parameters estimated from the model
			Proportion of new infections become chronic	Prevalence of cirrhosis at 20 years following chronic HCV	Covariates adjusted for in progression to cirrhosis	Transition probability (per year) from cirrhosis to		Transition probability (per year) to death from		Effect of antiviral therapy included	
						Decompensated Cirrhosis (DC)	HCC	DC (*Cirrhosis)	HCC		
Deuffic[79] France, 1999	Backcalculation using data on the natural history of HCV with estimates of the number of HCV-related HCC deaths	General population age & gender specific rates	70%	Estimated through model fitting	Age & Gender	Not modelled	4%	4%*	33%†	No	Model fitted to data on HCV-related HCC deaths 1979-95	(1) HCV-related HCC deaths 1979-2025
Law[80,101] Australia, 1999	Based on estimates of the incidence of IDU and incidence of HCV among IDUs	General population rates	75%	10.6% (6.7-13.3%)	None	Not modelled	¶	2.3%*	90%	No	None	(1) Prevalent number with HCV antibodies 1997; (2) Prevalent number with cirrhosis 1980-2010; (3) Incident number with HCC 1980-2010.
Wong[82] United States, 2000	Incidence not estimated; projections based solely on the estimated number of persons infected with HCV in 1991, with assumptions made regarding their stage of disease	General population age & gender specific rates, with excess mortality for IDUs and transfusion recipients	80%	23.5% (25% of chronic cases were assumed non-progressors)	Alcohol	4%	0.5%	‡	86%	No	None formally; although comparisons made with published studies of liver disease progression	(1) HCV-related liver deaths, 1992-2019
Zou[85] Canada, 2000	Incidence not estimated; projections based solely on the estimated number of persons infected with HCV in 1998, with assumptions made regarding their time of HCV acquisition	General population age specific rates	80%	31.4%	None	4%	1.5%	29.5%	NR	No	None	Incident & prevalent number of cases in 1998 and 2008 with (1) cirrhosis, (2) liver failure, (3) liver transplant, (4) HCC, (5) liver deaths.
Sagmeister[86] Switzerland, 2002	Past incidence not estimated; projections based on the estimated number of persons infected with HCV in 1998, with assumptions made regarding their stage of disease, and new infections thereafter estimated from the national reporting of acute HCV	General population age & gender specific rates	80%	18.9-21.9% (30-40% of chronic cases were assumed non-progressors)	None	4%	0.5%	‡	80% (70-90%)	Yes	Incidence of HCV-related HCC, death from HCV-related liver disease; and transplantation for HCV-related liver disease	Incidence of (1) HCC, (2) liver transplantation, (3) cirrhosis, (4) decompensation and (5) death related to HCV, 1998-2035.

NR Not reported; † Death from HCC; ‡ Different death rates were applied to cirrhosis states (i.e. ascites (11%); refractory ascites (33%); variceal hemorrhage (first year 40%, subsequent years 13%); hepatic encephalopathy (first year 68%, subsequent years 40%)); ¶ Rate of progression to HCC from infection assumed to be 10% of the rate to cirrhosis from infection

Table 1.3 (continued): Characteristics of HCV liver disease projection models published up to July 2004.

First author, Country, Year of publication	(i) Estimation of the past incidence of HCV infection	(ii) Account of mortality from causes unrelated to HCV	(iii) Assumptions used to model the progression of HCV disease								(iv) Data used to validate model results	(v) Parameters estimated from the model
			Proportion of new infections become chronic	Prevalence of cirrhosis at 20 years following chronic HCV	Covariates adjusted for in progression to cirrhosis	Transition probability (per year) from cirrhosis to		Transition probability (per year) to death from		Effect of antiviral therapy included		
						Decompensated Cirrhosis (DC)	HCC	DC (*Cirrhosis)	HCC			
Salomon[83] United States, 2002	Past incidence generated based on different assumptions regarding transmission through 3 main routes: mother-to-child, transfusion-associated, and community-infection (e.g. IDU)	2-5 times higher than the general population age & gender specific rates	60-90%	Estimated through model fitting	Age & Gender & Hepatitis B co-infection	3.0-6.0%	1.5-3.0%	14-40%	30-70%	No	Model fitted to data on (1) HCV seroprevalence 1988-1994 and (2) HCV-related HCC deaths 1970-1996	(1) HCV-related HCC deaths 1970-2000.
Davis[84] United States, 2003	Past annual incidence estimated from national reporting of acute HCV 1982-1995 (incidence for 1950-1981 was assumed the same as 1982)	General population age specific rates	79%	22.7% (27.5% of chronic cases were assumed non-progressors)	None	4%	0.5%	‡	86%	Yes	None formally, although comparisons made with data on prevalence of HCV infection	Prevalence of (1) HCV infection, (2) cirrhosis, (3) decompensation, (4) HCC, (5) liver-related death for 2000-2040.
Law[84] Australia, 2003	Based on estimates of the incidence of IDU and incidence of HCV among IDUs	IDU-related mortality assumed to be 1% per year; otherwise, general population age and gender specific rates applied	75%	7.1%	One third of chronic HCV cases were assumed to have faster progression	4%	1%	1.5%*	NR	No	None formally; although comparisons made with estimates of the number of IDUs and HCV infected persons	(1) Prevalent number with HCV antibodies by stage of disease, 1960-2001; (2) Prevalent number with cirrhosis 1990-2020; (3) Incident number with liver failure, HCC and HCV-related deaths to 2020.
Deuffic-Burban[79] France, 2004	Backcalculation using data on the natural history of HCV with estimates of the number of HCV-related HCC deaths	General population age & gender specific rates	75%	Estimated through model fitting	Age & Gender	Not modelled	Age-dependent	Age-dependent*	Age- and year-dependent	Yes	HCC deaths attributable to HCV 1979-98	(1) HCV-related deaths 1979-2070.
Sypsa[87] Greece, 2004	Past incidence not estimated; projections based on the estimated number of persons infected with HCV in 1991, with assumptions made regarding their time of infection, number of new infections remained stable after 1990 to 50% of the plateau observed in the late 1980s.	General population age & gender specific rates	80%	3.3%, 17.0%, 18.3%, 73.8%, 90.7% for persons aged 0-20, 21-30, 31-40, 41-50, >50 years at infection, respectively	Age	Not modelled	2.3%	2%*	58%†	No	None	Incident number of (i) cirrhosis; (ii) HCC, (iii) HCV-related deaths, 1990-2030.

† Death from HCC; ‡ Different death rates were applied to cirrhosis states (i.e. ascites (11%), refractory ascites (33%); variceal hemorrhage (first year 40%, subsequent years 13%); hepatic encephalopathy (first year 68%, subsequent years 40%)).

Figure 1.1: Diagram illustrating the division by chapters of the data which were used (a) as input parameters to and (b) to check the validity of the HCV projection model designed to estimate the current and future burden of HCV disease among injecting drug users (IDUs) in Glasgow and Scotland.

(a) Data used as input parameters to the HCV projection model:	**The incidence and cessation of injecting drug use each calendar year in Glasgow, 1960-2000** (derived by combining expert opinion with capture-recapture prevalence estimates described in Chapter 2); **and mortality from causes unrelated to HCV among current and former IDUs** (described in Chapter 6);	**The incidence of HCV infection among current IDUs in Glasgow, 1960-2000** (estimated through a HCV transmission model described in Chapter 3);	**The rate of HCV disease progression, including the influence of host factors age, gender, HIV co-infection and heavy alcohol use** (estimated through review of the literature and meta-analyses described in Chapters 5 & 6);

Aim of HCV projection model (detailed in Chapter 6):

Estimate the number of current and former IDUs who acquired HCV infection and progressed to mild, moderate and severe HCV disease in Glasgow and Scotland, 1960 - 2030

(b) Data used to check the validity of the HCV projection model:	**The prevalent number of current IDUs in Glasgow and Scotland** (based on capture-recapture estimates described in Chapters 2 & 6).	**The prevalence of HCV infection among current IDUs in Glasgow and Scotland** (based on survey data described in Chapters 3 & 6).	**The number of IDUs developing HCV-related decompensated cirrhosis each year in Glasgow and Scotland** (derived through a record-linkage study described in Chapter 4).

Chapter 2: Estimating the prevalence, incidence and cessation of injecting drug use in Glasgow 1960-2000: combining expert opinion with capture-recapture prevalence data

2.1 Introduction

Estimation of the size, and trends in the size, of injecting drug user (IDU) populations, locally and nationally, is fundamental to the planning and development of health-care services for this group[102,103]. Detection among IDUs of high prevalences of hepatitis C virus (HCV) infection (highlighted in Section 1.2), which can lead in the long-term to cirrhosis and hepatocellular carcinoma[104], has placed even greater emphasis on the importance of quantifying the dynamics of this population[12,105]. Data on the incidence and cessation of injecting drug use are essential if the future burden of HCV disease is to be predicted through statistical modelling initiatives.

Epidemiological studies of the epidemic spread of IDU in the United Kingdom (UK), generally, have been limited to those which use indirect methods to estimate prevalence for a specific calendar year[106]. Log-linear modelling of capture-recapture data was first applied in Glasgow[102] to estimate the prevalent number of current IDUs in 1989[107] (central estimate 9,420; 95% CI 6,960-11,880); further estimates were generated in 1990[18] (8,490; 7,490-9,720) and 2000[100] (7,190; 6,090-8,620). The city was thereby identified as being home to approximately a third of Scotland's IDUs[108] and having one of the highest IDU prevalences in Europe[19]. Few studies have attempted to derive estimates of the incident number of IDUs due to the shortage of appropriate data sources[109,110,111,112].

Lacking Scottish or UK data to generate an IDU epidemic curve for the past four decades (i.e. since the earliest reports of IDU), the use of expert opinion to elicit

one for Glasgow was investigated and presented in this chapter. Such elicitation has been used to gauge the prevalent number of IDUs in Australia[80,113] and Canada[114]. The study was confined to the Greater Glasgow Health Board area because of the added complexity of eliciting expert opinion at a national, rather than local, level and also due to the existence, for that area, of published data on IDU prevalence (as outlined above) to anchor experts' estimates.

2.2 Methods

2.2.1 Design and data collection

A modification of the Delphi technique, originally described by Dalkey[115], was used to reach consensus estimates on the prevalent and incident number of injectors and percentage ceasing IDU. Experts were defined as individuals whose extensive experience and knowledge about drug use was specific to Greater Glasgow. Five key informants, from different professions (academia, drugs service work, law enforcement, medicine, and sociology), were initially contacted to invite their participation and, in the first instance, nomination of other experts. All five informants were willing to participate and nominated a further 16 experts, who were subsequently contacted by telephone, where possible, or email to explain the study and to verify willingness to participate. The overall volunteer rate of experts was 95% (20/21): the five key informants and 15 of the 16 informant-nominated experts; one person refused because of concerns about the validity of the Delphi approach.

The 20 experts were asked, in May 2001, to complete anonymously a postal questionnaire (attached in Appendix, Section 2.5). The questionnaire asked for central estimates, and 90% certainty ranges, per quinquennium during 1960-2000 of (i) prevalence (i.e. "the number of people injecting drugs during each year"), (ii)

incidence (derived from two questions, which asked: (1) "relative to an arbitrary benchmark of 1,000 initiates into IDU in 1990, estimate the number of initiates in other years", and (2) "given that the benchmark of 1,000 initiates was chosen for convenience, estimate the actual number of initiates into IDU in 1990"), and (iii) cessation of injecting (i.e. "out of 1,000 injectors at the start of a calendar year, who survive throughout the year, estimate the number who would have permanently stopped injecting in that year"). In addition, participants were asked to return, separately from their completed questionnaire, a named postcard, indicating that they had completed and returned their questionnaire, which allowed reminders, at least two in the form of letters and emails, to be sent to non-responders during June-July 2001. As a mark of appreciation, participating experts were included in a prize draw, by way of the named postcard, for a £30 book voucher. Twelve of the 20 experts (5/5 informants and 7/15 informant-nominees) returned questionnaires by the end of August 2001. Unlike the classic Delphi technique[115], an iterative process was not used to refine these experts' opinions. Instead, results were compared with empirical estimates of the prevalent number of current injectors during 1990[18] and 2000[100] and an adaptation of rejection sampling[116] was substituted for the usual iterative process (described in Analyses below).

2.2.2 Background on experts

The professions of the 12 experts who returned questionnaires included academia, drugs service work, law enforcement, medicine and sociology. Participating experts reported their experience of the drug use field in Glasgow to be limited during the 1960s and 1970s, and knowledgeable during 1985 onwards. Key data sources which experts indicated had shaped their opinions were: (i) early reports of the rise in drug

use[117,118,119]; (ii) capture-recapture prevalence estimates[18]; (iii) hepatitis B virus reports (from the early 1980s)[120]; (iv) registrations of new attendances at drug services (only available for the 1990s and influenced by the increased capacity to treat drug users over time)[121]; and (v) their own observations and discussions with people working in the field. Prevalence estimates from capture-recapture studies (ii) were intrinsic to the assessment of experts' consensus (described below); furthermore, comparisons were also drawn with data from (i) and (iii) (see Discussion).

2.2.3 Analyses

Using S-PLUS software[122], data analysis consisted of:

(a) An examination of experts' estimates including the identification of outlying values; an expert's set of responses (i.e. central, lower and upper estimates) to either prevalence, incidence or cessation in a particular calendar year was regarded as outlying if the central estimate lay beyond the median 90% certainty range for all experts by more than 50%.

(b) Based on the restricted opinion of experts (i.e. with outlying values removed), their estimates were used to provide a single *consensus* distribution, which permitted the generation of an overall mean, median, and lower and upper 90% certainty limit for the three main parameters of (i) prevalence, (ii) incidence and (iii) cessation in each quinquennium. For each expert's reported range, their central value was assumed to be their most likely estimate for that parameter and, thus, a triangle distribution was applied to each expert's set of responses (i.e. central, lower and upper) for each parameter. A triangle distribution was used in preference to other standard probability distributions (e.g. normal or log-normal) due to the varying skewness of parameter estimates between experts. A *consensus*

distribution was then generated for each parameter by sampling 1,000 observations randomly from available experts' triangle distributions;

(c) To examine the coherency of experts' estimates, prevalences obtained from experts in (b)(i) and externally from other studies[18,100] were compared with a *constructed prevalence distribution* derived by combining expert data on incidence from (b)(ii) and cessation from (b)(iii) and accounting for 1-2% per annum mortality[123,124]. The following expressions were used:

$$p^{*}_{i,j} = \begin{cases} p_{i,j} & \text{for } i=1960; \quad j=1,...,1000; \\ p^{*}_{i-1,j} + q_{i,j} - ((r_{i,j} + s_{i,j}) \times (p^{*}_{i-1,j} + q_{i,j})) & \text{for } i=1961,...,2000; \; j=1,...,1000; \end{cases}$$

where, in a given calendar year i for the jth simulation,:

$p^{*}_{i,j}$ represents the prevalent number of injectors;

p_{1960_j} represents the prevalent number of injectors in 1960, which was randomly sampled from the prevalence distribution (b)(i) for 1960;

$s_{i,j}$ represents the mortality rate per annum, which was sampled from a uniform distribution with range 0.01 to 0.02;

$q_{i,j}$ and $r_{i,j}$ represent the incident number of injectors and proportion ceasing injecting, respectively, per annum, which were randomly sampled from the respective incident and cessation distributions, (b)(ii) and (b)(iii), in each quinquennial year, with values in between these years deduced from linear interpolation (note: variations on the linear assumption were explored);

(d) To derive *coherent estimates*, combinations of incidence and cessation values were sampled from the consensus distributions, generated in (b), and those which formed prevalence coherent both with published prevalence estimates (in 1990[18] and 2000[100]) and with experts' consensus on prevalence (in the remaining quinquennia) were retained. Following on from methods described in (c), values

of q, r and s were therefore rejected if the formulated prevalence did not fall within the 95% confidence limits of prevalence reported from capture-recapture studies in 1990 and 2000 and within the 90% certainty range of consensus distributions, (a)(i), generated from expert opinion in years 1960, 1965, 1970, 1975, 1980, 1985, and 1995.

2.3 Results

2.3.1 Experts' estimates: compliance and outliers

Prevalence, incidence and cessation estimates were provided by a mean of 9 (standard deviation 1.7), 9 (1.7), and 6 (2.0) experts, respectively, for quinquennia during 1960-2000. Three of the 12 experts consistently provided estimates well beyond the general consensus.

2.3.2 Experts' consensus estimates of prevalence, incidence and cessation

Table 2.1(i) and (ii) provide a summary of experts' responses, with outlying values removed. According to expert opinion, prevalence, incidence and cessation of IDU remained relatively low and stable during 1960-1975, rising several fold between 1975 and 1980 (3.3-4.0 times based on median prevalence; 5.5-8.8 times for incidence; and 5.0-6.0 times for cessation), rising again between 1980 and 1985 (4.7-5.0 times for prevalence; 1.9-2.4 times for incidence; and 1.2-1.3 times for cessation), and thereafter incidence declined marginally but prevalence and cessation both rose further.

2.3.3 Examining the coherence of experts' consensus estimates on prevalence, incidence and cessation

Figure 2.1 illustrates that the prevalence distribution (3), constructed from combining experts' consensus on incidence and cessation, corresponds well with experts' consensus on prevalence (1) during 1960-1980, but then underestimates, during 1985-2000, both their own consensus on prevalence (1) and also capture-recapture estimates (2).

2.3.4 Deriving coherent estimates on prevalence, incidence and cessation

Figure 2.1 also shows the coherence prevalence distribution (4) constructed from experts' consensus on incidence and cessation, using rejection sampling to filter out combinations which were not coherent with prevalence estimates from experts (1) and capture-recapture studies (2).

Table 2.1 summarises these data and highlights that experts had under-estimated the number of incident injectors in 1985, 1990 and 2000 (median consensus: 1,120, 1,095 and 948, compared to median coherence distribution: 1,335, 1,375 and 1,195, respectively) and also over-estimated the percentage of current injectors permanently ceasing injecting in four quinquennia during 1985-2000 (median consensus: 14%, 10%, 15% and 17%, median coherence distribution: 6%, 10%, 12% and 15%, respectively). From the coherence distributions, the incident numbers of injectors obtained in 2000 from 1,000 simulations were greater than those in 1990 and 1995 in 36% and 69% of cases, respectively. Similarly, the percentages ceasing injecting during 2000 obtained from 1,000 simulations were greater than those in 1990 and 1995 in 93% and 67% of cases, respectively.

The constraint imposed on prevalence in the rejection sampling process for the year 2000 was altered from the range 6,085-8,515, based on capture-recapture data[100], to 7,900-15,950 according to experts' consensus. This produced a coherent prevalence central estimate of 8,354 (90% certainty range 7,935-9,865) for 2000, which was still closer to that of the capture-recapture estimate (7,187) than that of the experts' central consensus (11,931).

2.4 Discussion

Models to estimate the future burden of HCV infection among injectors, recently acknowledged as a priority for future work in the Department of Health's "Hepatitis C Strategy for England"[125], require estimates of the number of people starting and ceasing to inject over time[80,108]. Whilst the importance of knowledge on incidence and cessation of IDU has long been recognised[105], few attempts have been made to estimate these in the UK[110,111] because of the limitations of available data sources which, generally, have been either incomplete in years or not representative of the whole population[121].

The first indication of an injecting epidemic in Glasgow was evident in the early 1980s when a sharp rise was reported in the number of people seeking treatment at hospitals for heroin addiction[118]. Further consideration of routine statistics and fieldwork data led Haw to estimate that there were approximately 5,000 problem drug users in Glasgow in 1983[119]. In the early 1990s, Frischer *et al.*, using capture-recapture methods which were applied to data from treatment centres, needle/syringe exchange schemes, HIV testing laboratories and the police in Glasgow, estimated a total of 8,490 (95% CI 7,490-9,720) current drug injectors[18]. Glasgow, a city with an extensively studied drug problem, has been at the forefront of IDU prevalence

estimation[102]; hitherto, however, no consensus had been sought on the size and shape of its IDU epidemic curve.

The Delphi approach, essentially, is a way to reach a consensus or a range of possible values for an uncertain parameter. The reliability of Delphi estimates, however, can only be judged in relation to other observed data. In previous studies, IDU prevalence estimates generated through the elicitation of expert opinion compared well with estimates derived using other methods. In Australia, Delphi estimates of the number of dependent injectors in 1997[80] were consistent, allowing for the difference in population groups, with estimates of the number of dependent heroin users, obtained through the use of three different methods (i.e. back-projection, capture-recapture, and multiplier)[113]. Similarly, Delphi estimates of the injector numbers in Toronto, Montreal and Vancouver during 1996 were of the same order as those obtained by capture-recapture methods[114]. All of these applications, however, relied on responses from relatively small groups of experts, which probably reflects the rarity of persons working in this field with sufficient knowledge and experience. This study was similarly weakened by the modest participation rate (12/21) of nominated experts, which illustrates the difficulty or reluctance experts had in quantifying parameters. However, this study differs in design from its predecessors[80,114], which did not report on elicitation of injector incidence and cessation, thereby enabling a check to be made, as here, on internal as well as external coherence.

Expert consensus on IDU prevalence indicated that the scale of the injecting problem in Glasgow had been minimal between 1960 and 1975 and epidemic throughout the 1980s. Whilst these findings conform with the reports outlined above[118,119], it must be highlighted that the early years, in particular 1960, 1965 and

1970, encountered the most non-responses from experts. This is likely to have been caused by either limited experience, problems with recall or lack of empirical data, which admittedly raises concerns about the reliability of the Delphi approach. Experts revealed that their estimates had also been shaped according to the rise in laboratory reports of hepatitis B virus infections during the early 1980s[120]. Figure 2.2 illustrates the sharp rise in these reports among those aged 15 to 24 years – indicative of the age at which IDUs commence injecting – during the early to mid 1980s, which aligns well with the estimated incident number of IDUs derived from this study. The number of HBV reports decreased during the late 1980s and 1990s as a result of reduced injecting risk behaviours[126] and vaccination against HBV.

For 2000, experts over-estimated the prevalence of IDU (median consensus 11,930; 90% certainty range 7,900-15,950) compared to that derived in a capture-recapture study (central estimate 7,190, 95% CI 6,090-8,620) published in September 2001[100]. Experts were unaware of the findings from the capture-recapture study for the year 2000 when they provided their opinions. The wide certainty range surrounding experts' central consensus on prevalence in 2000 reflected their difficulty in quantifying this unknown. The high prevalence reported by experts for 2000 may also have been influenced by a Needs and Resources Report[127] published in 2000, in which the number of Glasgow problem drug misusers (defined by the regular use – either *injecting* or *non-injecting* – of heroin, benzodiazepines, cocaine and/or amphetamines) was indicated, based on limited data and methods, to be in the range 12,400-15,400.

The collection of opinion on incidence and cessation of IDU in this study, although a challenge to experts (as indicated by the extent of non-responses and wide certainty ranges around parameters), provided an opportunity, not previously

explored, to combine these data and examine coherence with estimates of prevalence. Experts' opinions on prevalence, incidence and cessation were neither internally nor externally coherent, but coherence was enforced by an adaptation of rejection sampling. Through this process, experts were shown to have under-estimated the number of incident injectors and over-estimated the percentage ceasing injecting during 1985-2000. The simulations also indicated that whilst cessation of IDU had risen throughout the 1990s, a finding which is in keeping with the expansion of the methadone prescribing and other drug treatment services in Glasgow[128], there is however cause for concern at the rise in the incident number of injectors in the year 2000 compared to that in 1995.

The external point estimates and confidence intervals on prevalence were essential to anchor experts' opinions, although wide certainty ranges still remain around parameters; ideally, external data on incidence and cessation would have been incorporated, if available, into the rejection sampling process. Clearly, further efforts are required to collect data which will allow accurate estimation of the incidence and cessation of IDU both regionally and temporally. These data are necessary to inform policy-making, in terms of determining coverage and assessing the effectiveness of preventive measures and treatment options targeted at injectors.

Table 2.1: Expert opinion and generated distributions of prevalence, incidence and cessation of injecting drug use in Glasgow, 1960-2000.

Year	(i) Experts' estimates (outliers removed)			(ii) Consensus distributions, derived from experts' estimates*			(iii) Coherent distributions**		
	Central estimate Median (range)	Lower 90% certainty limit Median (range)	Upper 90% certainty limit Median (range)	Median / Mean	Lower 90% certainty limit	Upper 90% certainty limit	Median / Mean	Lower 90% certainty limit	Upper 90% certainty limit
Prevalent number of current injecting drug users (per year)									
1960	200 (35- 400)	20 (0- 300)	300 (50- 500)	173 / 197	28	432	149 / 158	31	355
1965	250 (50- 400)	40 (0- 300)	500 (60- 500)	267 / 240	45	460	276 / 280	137	431
1970	250 (100- 500)	50 (0- 400)	500 (200- 700)	258 / 300	61	586	429 / 421	268	565
1975	250 (100- 750)	100 (0- 500)	500 (200- 900)	324 / 357	89	750	557 / 548	329	725
1980	1000 (200- 2500)	500 (150- 1000)	2500 (250- 3500)	1074 / 1271	193	2694	1277 / 1370	529	2426
1985	5000 (4000- 8500)	4000 (2500- 7000)	6000 (5000- 9000)	5047 / 5342	3597	8372	4438 / 4830	3659	7327
1990	Capture-recapture estimate for this year (central estimate of 8494, 95% confidence interval 7490-9720) was provided to experts						8238 / 8346	7534	9565
1995	9750 (6500-13000)	8250 (5000-10000)	12000 (8000-16000)	9821 / 9850	6381	13226	7873 / 8151	6529	10689
2000	12000 (8000-15000)	10000 (6000-12000)	13000 (10000-19000)	11931 / 11845	7903	15948	6809 / 6955	6151	8228
Incident number of injecting drug users (per year)									
1960	30 (12- 38)	4 (0- 20)	50 (16- 75)	29 / 29	10	53	28 / 28	10	52
1965	30 (20- 50)	8 (0- 20)	45 (24- 75)	30 / 33	17	59	30 / 32	15	57
1970	40 (25- 75)	12 (0- 25)	53 (50- 75)	40 / 43	15	80	39 / 41	16	76
1975	80 (25- 200)	30 (0- 80)	75 (50- 500)	68 / 102	16	309	49 / 59	14	134
1980	438 (240-2000)	200 (160-1000)	1125 (320-2500)	599 / 772	203	2091	466 / 520	191	1026
1985	1063 (550-2000)	750 (500-1000)	1500 (1400-4000)	1120 / 1235	446	2684	1335 / 1671	861	3202
1990	1000 (750-1500)	800 (500-1000)	1450 (1200-3000)	1095 / 1144	641	1992	1375 / 1488	746	2438
1995	750 (560-1500)	450 (375-1000)	1219 (720-2000)	804 / 905	477	1636	841 / 935	481	1670
2000	1000 (562-1700)	550 (375-1000)	1350 (938-2000)	948 / 1008	523	1727	1195 / 1220	639	1811
Percentage of current injecting drug users permanently ceasing injecting (per year)									
1960	1 (1- 1)	1 (0- 1)	2 (2- 2)	1 / 1	1	1	1 / 1	1	1
1965	1 (1- 1)	1 (0- 1)	2 (2- 2)	1 / 1	1	1	1 / 1	1	1
1970	1 (1- 1)	1 (0- 1)	2 (2- 2)	1 / 1	1	1	1 / 1	1	1
1975	2 (1-10)	2 (0- 2)	3 (2-20)	2 / 4	1	14	2 / 5	1	15
1980	10 (10-25)	2 (0- 5)	20 (15-50)	12 / 16	5	39	13 / 17	6	40
1985	13 (5-25)	3 (0-15)	23 (7-50)	14 / 15	5	36	6 / 10	4	25
1990	10 (5-25)	8 (0-20)	15 (12-50)	10 / 16	5	36	10 / 8	3	13
1995	15 (10-30)	10 (0-25)	20 (15-50)	15 / 20	7	42	12 / 12	5	17
2000	20 (15-40)	13 (0-30)	34 (18-50)	17 / 25	14	45	15 / 15	11	18

* Distributions derived using methods described in Methods: Data Analyses (b).

** Distributions derived using methods described in Methods: Data Analyses (d).

Figure 2.1: Graph illustrating the distributions for the prevalent number of current injecting drug users derived from: (1) expert consensus, (2) capture-recapture studies, (3) combining expert consensus on incidence and cessation, and (4) combining expert consensus with capture-recapture data.

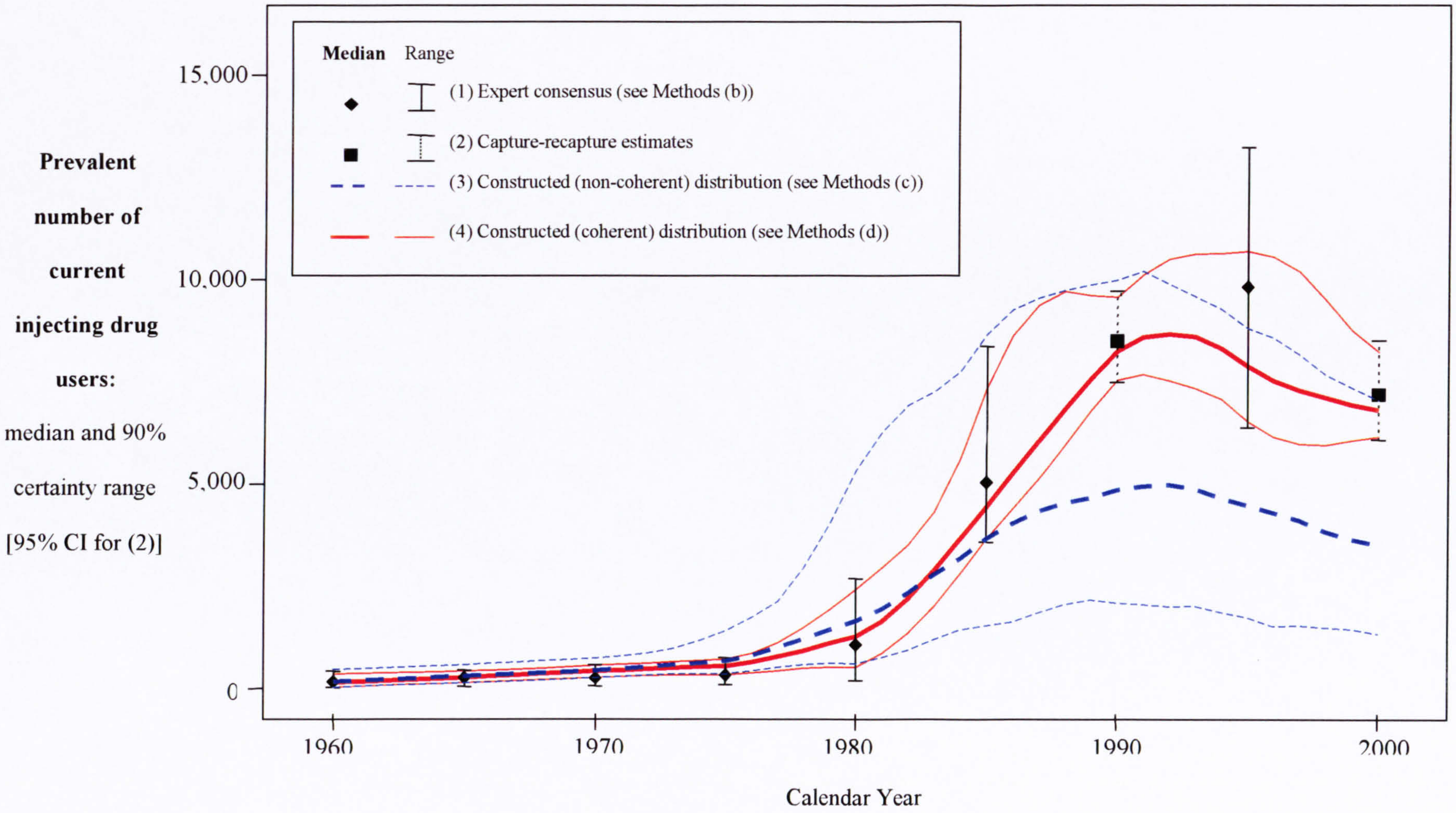
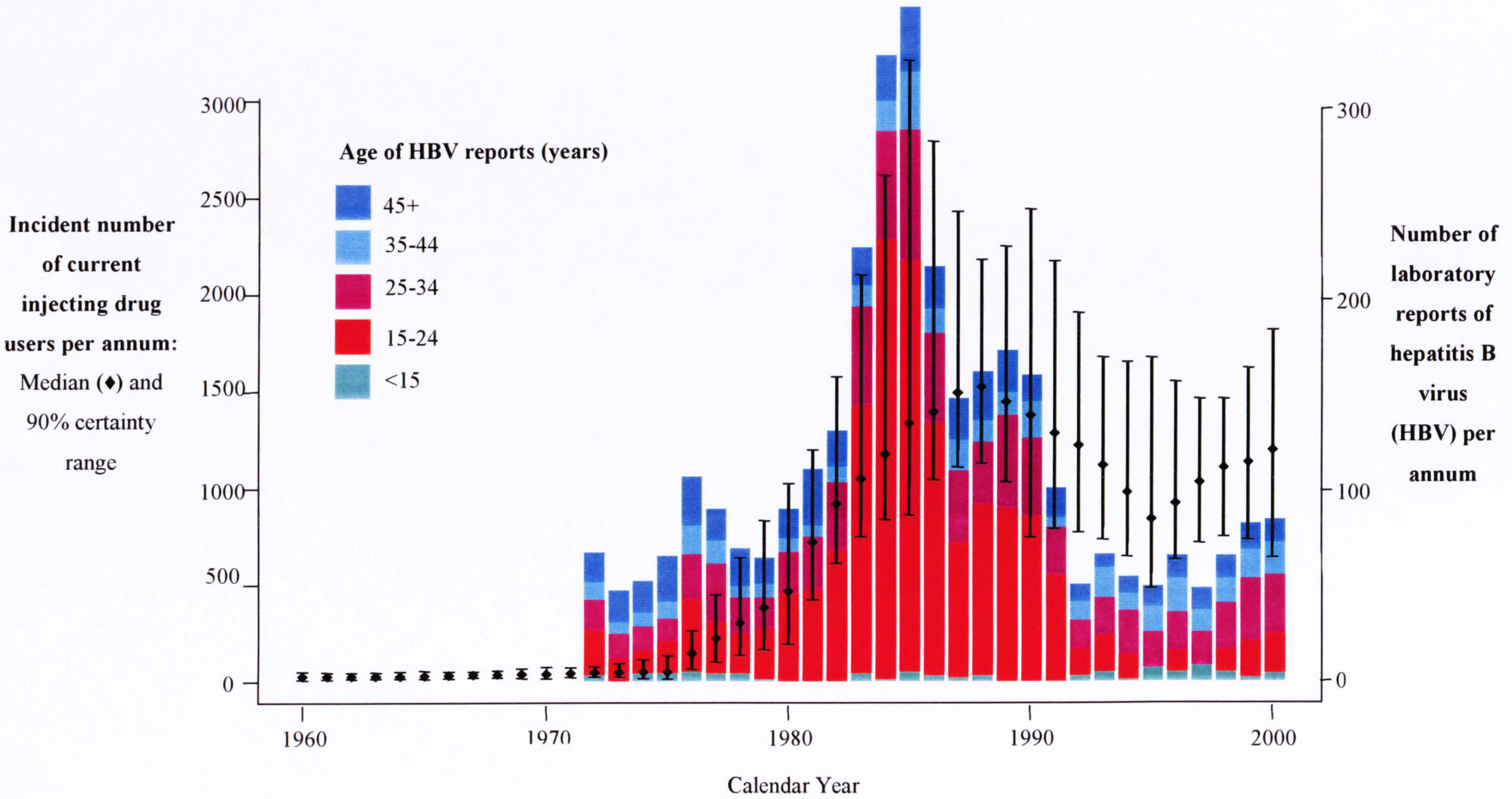


Figure 2.2: Graph illustrating the (coherent) distribution for the incident number of injecting drug users in Glasgow (1960-2000) and the annual number of laboratory reports of hepatitis B virus (surface antigen positive) cases in Glasgow by age (1972-2000).



2.5 Appendix: Questionnaire

Q1 Please indicate in the boxes **(1 = No, 2 = Yes)** your expertise related to the drugs field:

Academic ☐

Drugs worker ☐

Law enforcement ☐

Medical ☐

Sociological ☐

Q2 Please indicate your working experience and/or knowledge related to the field of injecting drug use in Glasgow in each of the following years: **(please use codes: 1 = Limited experience, 2 = Knowledgeable)**

GLASGOW	**1960**	**1965**	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**
Knowledge									

Q3 **(i) Please provide your estimate of the number of people injecting drugs in Glasgow for each of the years listed.**

In 1990, we have entered a benchmark figure for Glasgow (i.e. 8,500). You may overwrite this if you wish.

(ii) Please also provide a 90% certainty range for each estimate**: i.e. an upper and lower limit, so that you are 90% certain that the number of people injecting drugs in that year was between these limits.**

GLASGOW	1960	1965	1970	1975	1980	1985	1990	1995	2000
(i) Number injecting							**8,500**		
(ii) 90% certainty range									

(iii) In addition, please estimate the percentage of injectors in each of these years who were injecting drugs, on average, on a daily basis.

(iv) And please provide a 90% certainty range for your estimates in (iii)**: i.e. an upper and lower limit, so that you are 90% certain that the percentage of injectors who were injecting drugs on a daily basis was between these limits.**

GLASGOW	1960	1965	1970	1975	1980	1985	1990	1995	2000
(iii) % injecting daily									
(iv) 90% certainty range									

Q4 For reference, a benchmark of 1,000 new initiates into injecting drug use has been set for Glasgow in 1990. Relative to the 1,000 new initiates in 1990, please give your estimate (with 90% certainty range) of the number of new initiates into injecting drug use in each of the other years listed:

GLASGOW	**1960**	**1965**	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**
(i) Number of new initiates							**1,000**		
(ii) 90% certainty range									

Q5 The benchmark of 1,000 initiates in 1990 was chosen for convenience in the previous question. We now ask you to provide your own estimate (with 90% certainty range) of the actual number of new initiates into injecting drug use in 1990 for Glasgow :

(i) Estimate for 1990 .....

(ii) 90% certainty range .....

Q6 Out of 1,000 injecting drug users at the start of a calendar year, who survive throughout the year, how many do you estimate (with 90% certainty range) would have permanently stopped injecting in that calendar year?

GLASGOW	**1960**	**1965**	**1970**	**1975**	**1980**	**1985**	**1990**	**1995**	**2000**
(i) Number stopped injecting									
(ii) 90% certainty range									

Q7 Please tell us about any years in which you think the number of people injecting drugs in Glasgow may have increased sharply:

Year(s) of sharp increase .....

Q8 Please tell us about any years in which you think the number of people injecting drugs in Glasgow may have decreased sharply:

Year(s) of sharp decrease .....

Q9 Briefly indicate any key data sources that shaped your opinions; and make any other general comments that you wish?

We thank you for your time and effort in answering our questionnaire.

Chapter 3: Modelling the spread of hepatitis C virus infection among injecting drug users in Glasgow 1960-2000

3.1 Introduction

Injecting drug users (IDUs) are at high risk of acquiring hepatitis C virus (HCV) infection through the multi-person use of injection equipment, principally needles/syringes[129]. High seroprevalences of HCV antibodies, in the range 50-90%, have been detected in surveys of IDUs throughout the developed world[12,130]. HCV, generally, has a long and variable asymptomatic incubation period before it causes severe liver disease[131]. The enormous health and economic burden this infection presents is increasingly being recognised[80,82].

HCV has been circulating among IDUs in Scotland since at least the early 1980s[20] when there were reports of a rapid rise in the number of IDUs in Glasgow[118,120], Scotland's largest city. In 1990, Glasgow had approximately 8,500 IDUs[18], almost half of Scotland's injecting population[108], and one of the highest population prevalences (2.7% of 20-29 year olds) in Europe. The prevalence of HCV antibodies among IDUs, having reached 74% by 1990-91[47], suggests that HCV spread rapidly throughout this population during the 1970s/1980s. During the 1990s, an ecological association between reductions in HCV prevalence and the development of harm reduction initiatives was evident[47,132]; nevertheless, the incidence of HCV remained high in 1999/2000[50].

Because of the extent of the past, current and likely future burden of HCV – and the wealth of available epidemiological data – it was considered both necessary and feasible to model the relationship between needle/syringe sharing and the incidence of HCV among IDUs in Glasgow during 1960-2000. This model would

inform on the past incidence of HCV infection in this population and permit the gauging of changes in risk behaviours required to effect appreciable reductions in the incidence of HCV infection. Such insights will inform those responsible for developing new ways to prevent HCV transmission among IDU populations.

3.2 Methods

3.2.1 Overview

Stochastic modelling was used to simulate (day by day) the transmission of HCV, during 1960-2000, through the sharing of used needles/syringes among current IDUs, on an individual basis, from their onset of injecting drug use. Individuals were given the potential to progress through three states of infection: susceptibility, acute and chronic. As detailed below, the models were designed to use available information on (a) the incidence and cessation of injecting drug use in Glasgow (*population factors*), (b) the frequencies with which Glasgow IDUs injected and shared needles/syringes, and the numbers of different persons they shared with (*behavioural factors*) and (c) the susceptibility, transmissibility and carriage of HCV infection (*viral factors*). Generated outcomes were (i) estimates of the actual prevalence and incidence of HCV infection (from needle/syringe sharing) during 1960-2000 and (ii) scenario data on the prevalence and incidence of HCV infection during 1988-2000 assuming that there had been either no or more effective interventions to reduce needle/syringe sharing. Models were developed using S-PLUS software[122].

3.2.2 Model design

3.2.2.1 Population factors: *Incidence and cessation of injecting drug use*

Previously, in Chapter 2, estimates of the size of Glasgow's active IDU pool in 1960 and the number of individuals who entered (i.e. commenced injecting) and who left (i.e. either permanently stopped injecting or died) this pool each calendar year thereafter till 2000 were generated through a modified Delphi approach which combined expert opinion with capture-recapture prevalence data. Figure 3.1 illustrates the estimates of (a) the incident number of IDUs and (b) the percentage ceasing to inject in Glasgow per annum during 1960-2000 which, together with an assumed 1-2% per annum mortality rate[123], provided estimates of the prevalent number of IDUs per annum as shown in Figure 3.1(c). Ten percent of the actual population size was used in the simulations to reduce the computer time required to process data; as a sensitivity check, simulations were also performed at 30% of the actual population size and produced comparable findings. We assumed that individuals entered and left the IDU pool on random days throughout a year; IDUs were randomly selected with equal probability to leave the pool.

3.2.2.2 Behavioural factors

3.2.2.2.1 *Sources of data*

Two principal sources of needle/syringe sharing data were available: multi-site, community-wide surveys undertaken in Glasgow during 1990-1994 and 1999[51,133], and those performed in Edinburgh – Scotland's capital city, 70km from Glasgow – during 1992-1993[126]. The former provided estimates of injecting and needle/syringe sharing (injecting with needles/syringes previously used by someone else) frequency and numbers of persons shared with during the previous six months (adjusted to

twelve months, explained in footnote to Figure 3.2), while the latter provided, for every year since 1980, estimates of the proportions of injectors who had shared at least once. A study comparing behaviours among IDUs in Edinburgh and Glasgow[134], undertaken in 1985, indicated that the proportions sharing at least once in both cities were very similar; accordingly, the above Edinburgh data were used as a surrogate for sharing behaviour in Glasgow during the 1980s (note: only data on the proportion sharing at least once were used; data on the numbers of partners were not exchangeable because Edinburgh IDUs had a much greater number than Glasgow's IDUs[134]). No needle/syringe sharing data were available for the period prior to 1980.

The following behavioural sections describe the model process each year for generating (a) the frequency with which IDUs injected drugs, (b) the percentage of IDUs who had shared a needle/syringe, (c) the number of needle/syringe sharing partners, (d) the assignment of number of needle/syringe sharing partners to each IDU, (e) the selection of actual needle/syringe sharing partners for each IDU, and (f) the frequency with which IDUs shared needles/syringes.

3.2.2.2.2 *Frequency of injecting*

Glasgow IDUs reported a high and consistent frequency of injecting (from 1990-1994 surveys: 23% injected less than twice a day and 77% injected at least twice a day[133]). For simplicity, we assumed that all IDUs injected three times per day for 48 weeks per year, thus accounting for four weeks' abstinence from injecting[135]; abstinence was increased to 12 weeks during 1995-2000, an adjustment based on survey data[51], which correlates with an increased prescribing of methadone to IDUs[124]. On a given day, the number of times an individual shares needles/syringes from their three injections was randomly assigned using a binomial distribution with probability equivalent to the

proportion of their injecting episodes spent sharing (see "*Frequency of needle/syringe sharing*", 3.2.2.2.7 below). Then, for each sharing occasion, the partner from whom they receive their used needle/syringe was randomly selected from their group of sharing partners; if the selected partner was an HCV carrier, transmission occurred with probability as described below (see "*Transmissibility*", 3.2.2.3.2 below).

3.2.2.2.3 *Percentage of IDUs per year who had shared a needle/syringe at least once*

The percentage of IDUs who were assigned to share a needle/syringe at least once during a particular calendar year in the model was generated by sampling from a uniform distribution, where limits were varied in four epochs: 1960-1976 (a period of minimal injecting), 1977-1985 (a period of injecting epidemic growth), 1986-1990 (a period of HIV awareness and introduction of harm reduction initiatives), and 1991-2000 (era of harm reduction). Based on observed data for Glasgow and Edinburgh (Figure 3.2), rates in the ranges 70-89% and 35-49% were used for the respective periods 1977-1985 and 1991-1997, and a linear reduction in the range was applied during the intermediate epoch. A range of 40-54% was applied in years 1998-2000 to reflect the recent rise in needle/syringe sharing observed in Glasgow[51]. Data on the behaviours of IDUs during the 1960s/1970s were not available; therefore, a broad range of 50-89% was applied to encompass the prevalence of needle/syringe sharing in the first epoch 1960-1976.

3.2.2.2.4 *Number of needle/syringe sharing partners*

The number of IDUs with whom Glasgow respondents reported needle/syringe sharing at least once in the previous six months (referred to as partners) is shown in

Figure 3.3; very few respondents reported more than 20 partners. The number of partners reported by respondents was heavily skewed, with a mean of 3 and 2 partners reported in the 1990 and 1991-1994 surveys, respectively; a survey of IDUs attending general practices in Glasgow during the early to mid 1980s revealed a mean of 8 partners (range 1-30)[134]. Geometric distributions, as illustrated in Figure 3.3, were used to generate the number of partners, $x_{i,k}$, for the pool of needle/syringe sharing IDUs each year (see Appendix in Section 3.5.1). The mean number of partners amongst IDUs who were assigned to share needles/syringes each year was assumed to be eight, two and three during the periods 1977-1985, 1991-1997 and 1998-2000, respectively; a linear reduction in the mean number of partners was employed during 1986-1990. Due to the low prevalence of IDUs in the earlier period 1960-1976, a conservative mean of two partners was applied.

3.2.2.2.5 *Assignment of number of needle/syringe sharing partners to each IDU per annum*

In any given year k, a vector for the number of partners, denoted as $x_{i,k}$, was generated (described above) and each element of $x_{i,k}$ was assigned to a person in the pool of n_k IDUs through a process of either random (i.e. equal probability) or weighted selection. The latter refers to an increased likelihood of an IDU selecting a number of partners, in a given year, which is the same or near to the number of partners they had been assigned in the previous year (see Appendix in Section 3.5.2).

3.2.2.2.6 *Selection of actual needle/syringe sharing partners for each IDU per year*

At the beginning of each year in the model, for individuals who were assigned a lower number of partners than in the previous year, established partnerships would be randomly deselected. The remaining established partnerships would be retained for that year, and others formed until the required number of partnerships was reached. An IDU selects their actual partner(s) based on either random or weighted selection, where the latter refers to an increased likelihood of an IDU selecting a partner who has the same or near to the same "number of partners" as they have in that year (see Appendix in Section 3.5.3).

3.2.2.2.7 *Frequency of needle/syringe sharing*

The frequency with which Glasgow IDUs shared needles/syringes correlated strongly with the number of sharing partners reported (Figure 3.4). For each calendar year in the model, individuals were randomly assigned a frequency of sharing, according to the number of partners they had, based on the Glasgow 1990-1994 data; for example, for IDUs with one sharing partner, 49%, 33%, 4%, 2%, 2%, 1%, 0%, 1%, 0%, 0% and 8% recipient-shared needles/syringes for 0.5%, 5%, 15%, 25%, 35%, 45%, 55%, 65%, 75%, 85% and 95% of their injecting episodes, respectively.

3.2.2.3 Viral factors

3.2.2.3.1 *Susceptibility*

All new initiates to injecting who entered the IDU pool were regarded as being susceptible to infection (Figure 3.5). HCV has been circulating for many decades; thus, an IDU from the original pool in 1960 was randomly assigned as an HCV carrier

allowing them to transmit the virus to others. A susceptible individual was considered to have been exposed to HCV only when he/she injected with a needle/syringe previously used by an individual who was an HCV carrier. Transmissions through other routes, such as sexual intercourse[136], occur relatively infrequently and thus these were not considered in the model.

3.2.2.3.2 *Transmissibility*

Upon exposure to HCV, the probability of an individual becoming acutely infected was assumed to be, on average, 2-3% (range 0-10%), based on reported rates of transmission occurring among health care workers after needle-stick injuries[137,138]. A beta distribution (mean 0.03, variance 0.0001) was used to generate probabilities for transmission after each exposure. A short period (6-8 weeks) of high viraemia[139] follows infection with HCV, a phenomenon similar to that observed for HIV; using knowledge which exists for HIV[140,141], but not HCV, the effect of a 10-fold increase in infectivity during the initial high viraemia phase was explored. During acute infection, HCV RNA – indicating infectiousness – has been detected in blood within two weeks of exposure[142]; accordingly, in the model, individuals became infectious two weeks post infection.

3.2.2.3.3 *Carriage*

Of individuals with newly acquired HCV, between 15-40% spontaneously recover from their acute infection, generally within two years[3,4]. A beta distribution (mean 0.25, variance 0.001) was used to generate probabilities for viral clearance among newly infected individuals and a geometric distribution (parameter 1/290 days) was used to generate intervals from infection to recovery. Partial immunity against HCV

re-infection and persistence may be acquired in individuals who have had previous infection and cleared their virus[143,144]. Thus, in the model, individuals who recover from their acute HCV infection re-entered the susceptible population, but, according to Farci et al.[143], were half as likely to develop new viraemia following re-exposure and were twelve times less likely to develop chronic infection following acute status. Individuals who do not recover from their acute infection develop chronic HCV and remain infectious.

3.2.3 Model outcomes

3.2.3.1 Prevalence of HCV infection

The prevalence of HCV antibodies among current IDUs each year between 1960 and 2000 was simulated. Different models were specified to assess the effect on HCV seroprevalence of (i) increasing the infectivity of newly HCV infected individuals during the short period of high viraemia following seroconversion, (ii) weighting the assignment of number of sharing partners to each IDU, and (iii) weighting the selection of actual partners for each IDU. For each model, 100 simulation runs were performed; HCV seroprevalence was summarised by reporting the 10^{th}, 50^{th} and 90^{th} percentiles separately for each year.

The fit of models was determined by comparing modelled with observed HCV seroprevalences at different calendar years: principally, community-wide surveys of Glasgow IDUs reported that HCV seroprevalence declined between 1990 (79%) and 1999 (61%)[47]. HCV seroprevalence estimates were also available from IDUs who had tested hepatitis B surface antigen positive and negative in 1973-80 (81% and 65%, respectively) and positive in 1984 (65%) (Personal communication: Sheila Cameron, Glasgow Regional Virus Laboratory).

3.2.3.2 Incidence of HCV infection

The incident number of HCV infections each year was obtained from the models for susceptible current IDUs who either (i) had no previous infection or (ii) had cleared their previous infection; for (i), the incidence was calculated as the number of new infections during the year divided by the total number of injector-years contributed by HCV antibody negative IDUs.

3.2.3.3 Potential impact of harm reduction measures on the prevalence and incidence of HCV infection

Data on HCV incidence were generated by applying the high levels of needle/syringe sharing from the early to mid 1980s in Glasgow to the period 1988-2000. By comparing models with and without this high risk behaviour, estimates of the number of HCV infections averted among Glasgow IDUs during the period of harm reduction (1988-2000) were obtained.

3.2.3.4 Potential impact of hypothetically lower risk behaviours on the prevalence and incidence of HCV infection

The impact of the following hypothetical reductions in risk behaviour, for the period 1988-2000, on the prevalence and incidence of HCV was examined:

(i) the percentage of IDUs who had shared per year was reduced to 1-10%, 11-20%, 21-30%, 31-40%, and 41-50% (from the estimated actual rates, described above in 3.2.2.2.3, of 45-79%, 35-49% and 40-54% in years 1988-1990, 1991-1997 and 1998-2000, respectively);

(ii) the mean number of needle/syringe sharing partners per annum was reduced to 1, 1.5 and 2 (from the estimated actual numbers, described above in 3.2.2.2.4, of 3-6, 2 and 3 in years 1988-1990, 1991-1997 and 1998-2000, respectively);

(iii) the percentage of injecting episodes shared was reduced to below 10% (from that illustrated in Figure 3.4).

3.3 Results

3.3.1 Modelled prevalence of HCV infection

Significantly more simulations generated by model (a), which employed a ten-fold higher infectivity to newly HCV infected IDUs during the short period of high viraemia following seroconversion, than by model (b), without the higher infectivity constraint, produced HCV seroprevalences in the ranges of those obtained through community-wide surveys of Glasgow IDUs in years 1990-1993 (56-92%), 1994-1996 (53-86%) and 1999 (50-75%) (Figure 3.6) (87% compared to 55% of 100 simulations, respectively; p=0.0001). The best fitting model (a) was used below to estimate the incidence of HCV infection and to examine changes in this with different scenarios of higher and lower risk behaviour.

The process of assigning sharing partners to each IDU per year was weighted (described in Methods and Appendix 3.5.2-3.5.3, such that the mean *z* score for years 1977-1987 ranged 1.4-2.4 (versus 5.4-6.9) under weighted (versus random) selection, and for years 1991-2001 ranged 0.4-0.8 (versus 1.1-1.9)), but the effect on HCV seroprevalence was marginal: for years 1977-1987, median ranged 70-80% (versus 74-77%) under weighted (versus random) selection; and for years 1991-2000, median ranged 57-61% (versus 62-69%) under weighted (versus random) selection.

3.3.2 Modelled incidence of HCV infection

The annual incident number of HCV infections among current IDUs in Glasgow was estimated, by model (a), to be low during 1960-1976 (median new infections among IDUs who had no previous infection and had cleared their previous infection: 10-60 and 0-20 per annum, respectively), rising steeply during the early 1980s to peak in 1985 (1,120 and 210, respectively), stabilising during 1991-1997 (510-610 and 100-140, respectively) and rising again during 1998-2000 (710-780 and 130-150, respectively) (Figure 3.7).

The median percentage of HCV antibody negative IDUs who acquired new HCV infection per annum was estimated to be in the ranges 5-27%, 43-48% and 14-20%, which corresponds to incidences of 6-40, 78-89 and 18-30 per 100 susceptible injector-years, during periods 1960-1976, 1977-1986 and 1990-2000, respectively (Figure 3.8).

3.3.3 Potential impact of harm reduction measures on the prevalence and incidence of HCV infection

Carrying forward the high levels of needle/syringe sharing from the early 1980s to 1988-2000 generated higher prevalences of HCV during this latter period (median 83-91%) than were determined through model (a) with the lower estimated actual levels of needle/syringe sharing among Glasgow IDUs (62-75%) (Figure 3.6 (c) and (a), respectively). The median cumulative number of newly HCV infected IDUs during 1988-2000 in Glasgow from models (c) and (a), with and without the higher levels of risk behaviour, were 13,420 and 8,910 (10^{th} to 90^{th} percentiles: 11,370-16,290 and 7,720-10,340), respectively, which indicates that potentially as many as 4,500 (2,400-7,700) HCV infections had been prevented as a result of established harm reduction

measures during this period – that is, around half as many prevented as actually occurred.

3.3.4 Potential impact of hypothetically lower risk behaviours on the prevalence and incidence of HCV infection

Reductions in three key risk parameters – (i) the percentage of IDUs who had shared a needle/syringe per year, (ii) the mean number of needle/syringe sharing partners per year, and (iii) the percentage of injecting episodes shared – all impacted on the prevalence and incidence of HCV infection by varying amounts (Figure 3.9). Assigning either 1-10%, 11-20%, 21-30%, 31-40% or 41-50% of IDUs to have shared a needle/syringe per year during 1988-2000 would have reduced the HCV prevalence to a median of 18%, 33%, 46%, 55% and 63%, respectively, and the incidence to a median of 1, 7, 14, 20 and 28 infections per 100 susceptible injector-years, respectively, by the year 2000; while the median cumulative number of newly HCV infected IDUs during 1988-2000 would have been 1,310, 3,700, 5,860, 7,550 and 8,960, respectively.

Alternatively, assigning the mean number of partners per annum to 1.0, 1.5 and 2.0 during 1988-2000 among needle/syringe sharing IDUs would have reduced the HCV prevalence to a median of 33%, 48% and 58%, respectively, and the incidence to a median of 5, 13 and 21 infections per 100 susceptible injector-years, respectively, by the year 2000; the median cumulative number of newly HCV infected IDUs during 1988-2000 would have been 3,650, 6360 and 7,990, respectively. Finally, limiting the percentage of injecting episodes shared to less than 10% among needle/syringe sharing IDUs during 1988-2000 would have resulted in a median HCV prevalence of 48% and incidence of 14 infections per 100 susceptible injector-years

by 2000; the median cumulative number of newly HCV infected IDUs during 1988-2000 would have been 6,280. As changes in one risk parameter will likely correlate with changes in another, these findings may have under-estimated the collective effect of reduced risk behaviours on HCV prevalence and incidence.

3.4 Discussion

This chapter presents the findings of a model designed to estimate the impact of established, and hypothesised, harm reduction interventions on HCV incidence by simulating the transmission of HCV among Glasgow IDUs according to their self-report of needle/syringe sharing. Since the introduction, in the late 1980s, and continual expansion, during the 1990s, of needle/syringe exchanges and other harm reduction interventions targeted at IDUs, reductions in both needle/syringe sharing[145] and the incidence of HCV[47,50] have been evident in Glasgow. It is possible that some of the behaviour change resulted independently of the harm reduction activities; however, with several studies undertaken in Glasgow and elsewhere demonstrating a strong association between HCV prevalence reduction and harm reduction initiatives[146], it is plausible that such interventions were responsible for averting, during 1988-2000, many of the 4,500 HCV infections (10^{th} and 90^{th} percentiles: 2,400-7,700) indicated by scenario analysis.

Full advantage of available behavioural and epidemiological data was taken to model the heterogeneity typical of an entire IDU population. Inevitably with a model designed to reproduce a complex process, there were limitations which need to be considered: (i) biases may exist as a result of IDUs' under- or over-reporting risk behaviour, although previous studies have found IDUs to be generally reliable in their self-report of this[147,148,149], and findings from the Glasgow surveys have been

corroborated by other investigations[150]; (ii) a broad range for needle/syringe sharing was applied in the 1960/1970s epoch to allow for the absence of data, but this did not hinder the estimation of the incident number of HCV infections because so few individuals were injecting during this period; (iii) previous infectious disease models among IDUs have been limited by the lack of data on the changing size of this population[151]; whilst this model was designed to allow individuals to enter and leave the current IDU population, further data are needed to corroborate our estimates on the incidence and cessation of injecting drug use; (iv) IDUs were all posed with an annual mortality rate in the range of 1-2%, although recent work has indicated that IDUs' mortality is higher for males and increases with age[152]; (v) behavioural data specifically on the change in needle/syringe sharing partners from one timeframe to the next and the propensity to share with different partners are needed to refine the model; importantly, weighted selection employed to minimize the change in number of partners from one year to the next per IDU did not affect model results. Future modelling also needs to consider differences in risk behaviour in the initial versus subsequent years following onset of injecting drug use[133]; (vi) individuals were only exposed to HCV through the sharing of needles/syringes; it has been suggested that HCV can be contracted through other injecting equipment[153], but only limited evidence of transmission efficiency for this exists[154,155]. Since infections occurring through means other than needle/syringe sharing, including unprotected sexual intercourse and tattooing, were judged to be relatively small and the behavioural data for these were not available, they were not considered in this model (as in previous HCV transmission models among IDUs[156,157]); (vii) the cleaning of used needles/syringes and its influence on HCV transmission, believed to be considerably less-effective than with HIV[157], was not considered; (viii) while the aim was to

capture the behavioural heterogeneity of IDUs, it is appreciated that the detailed data requirements of the model will influence its generalizability.

Despite these limitations, modelled data on HCV prevalence agreed well with observed trends among current IDUs in Glasgow. The model which discounted the effect of higher infectivity among newly HCV infected IDUs, a criticism of previous HCV transmission models[158], under-estimated the prevalence of HCV during the 1990s compared to data from community-wide surveys of Glasgow IDUs. The lower than expected HCV prevalences could be explained by the omission of transmissions occurring through other routes such as indirect sharing of injecting equipment. Alternatively, considering higher infectivity during acute viraemia after infection in the model produced HCV prevalences consistent with survey data, and suggests that this phenomenon is an important factor in the spread of HCV, as recognised with HIV[140,141].

Further validation of the behavioural assumptions used in the model was attained by adapting the viral characteristics to monitor the spread of HIV among IDUs in Glasgow (details provided in Appendix, Section 3.5.4). This showed that the prevalence of HIV remained low and stable (median of 0.4-1.0% during years 1983-2000; 10th and 90th percentiles ranged 0-0.3% and 2.3-7.9%, respectively); a finding that is consistent with detected rates among Glasgow IDUs[159]. Corroborating a previous modelling application in Australia[157], these results demonstrate that the ten-fold higher infectivity of HCV compared to HIV[129,160] largely explains the difference in the spread of these two viruses among IDUs.

Observed data on HCV incidence among IDUs in Scotland are confined to the 1990s and have been derived from cross-sectional (centrally estimated 20-27 per 100 person-years among recent-onset IDUs[108]) and cohort studies in selected populations

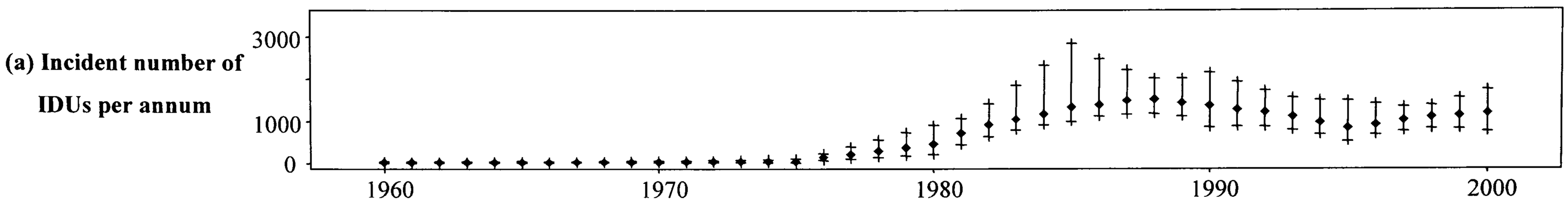
(28 per 100 person-years; 95% CI 16-51[161]), which compare favourably with our modelled estimates of HCV incidence during the same period (18-30 per 100 susceptible injector-years). The incident numbers of IDU-related HCV infections estimated historically are central to the development in Chapter 6 of models to project the number of people likely to progress to HCV disease in the future[80,108].

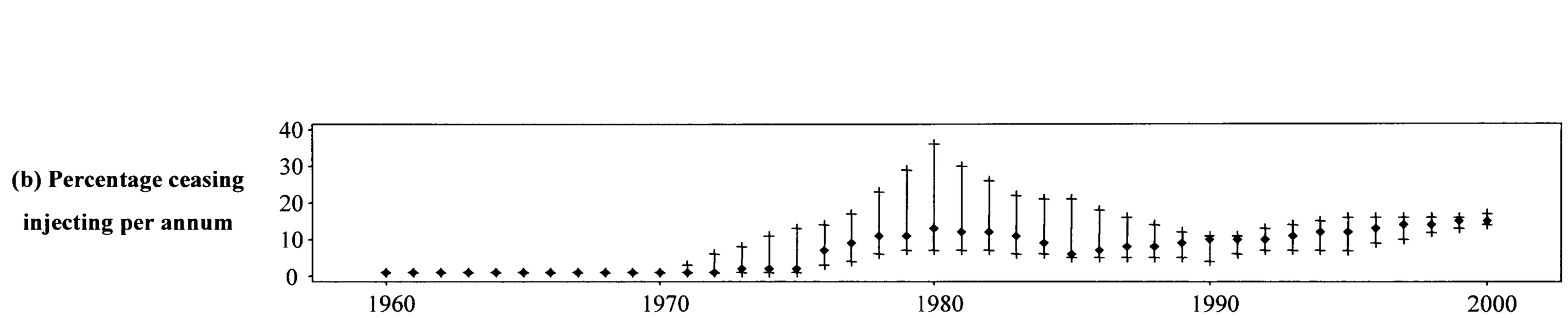
HCV transmission thus continues to occur at an alarming rate among Glasgow's IDUs. The main public health message – "not to share needles/syringes" – used in this population to control HIV transmission has proved inadequate for the control of HCV. A previous study had indicated that improving IDUs' access to sterile injecting equipment is likely to result in reductions in sharing[133]; accordingly, research is underway in Glasgow to determine the effect on behaviours of removing government restrictions on the numbers of needles/syringes distributed. We cannot ignore, however, that some IDUs share needles/syringes despite having sufficient access to harm reduction services. Our model indicates directions for public health strategies to reduce the incidence of HCV infection. Incidence can be more successfully reduced if IDUs who, unavoidably, share needles/syringes confine their borrowing of used equipment to one person, ideally someone they know well and who has recently tested HCV antibody negative; with this strategy alone (i.e. reducing the mean number of partners to one during 1988-2000), an estimated 5,300 HCV infections (10^{th} and 90^{th} percentiles: 4,100-6,700) could have been averted during 1988-2000 among Glasgow IDUs. Alternatively, permitting only 11-20% of the IDU population to share a needle/syringe annually during 1988-2000 would have similarly averted an estimated 5,200 HCV infections (10^{th} and 90^{th} percentiles: 4,200-6,600). Determining the most effective means of communicating risk reduction strategies to IDUs should be a priority in HCV prevention plans. The ability of existing HCV

testing and counselling practices to change behaviour and prevent further transmission among IDUs remains unclear[162,163]. A thorough evaluation of such services[164] is required to determine if the HCV testing of current IDUs should be promoted.

Based on a study which examined the direct medical costs associated with HCV infection among IDUs in Australia[76], the estimated 550 to 920 new HCV infections among IDUs in Glasgow during 2000 could equate to approximately three to five million pounds in health care spending in the future as sequelae become manifest. A serious commitment to model in advance, implement and audit strategies, which could achieve appreciable reductions in risk behaviours and HCV transmission among IDUs, is urgently needed to influence the future course of this epidemic. Otherwise the mounting HCV burden of illness and cost will continue. Meanwhile, "off-injecting" remains a key public health message both for HCV prevention and treatment. Behavioural surveillance of IDUs should also be expanded to keep abreast of potential changes in blood-borne virus transmission and inform HCV prevention efforts.

Figure 3.1: Estimates (10^{th}, 50^{th} and 90^{th} percentiles per annum) of (a) incidence, (b) cessation and (c) prevalence of injecting drug use in Glasgow during 1960-2000, generated from a modified Delphi study presented in Chapter 2 (Table 2.1).





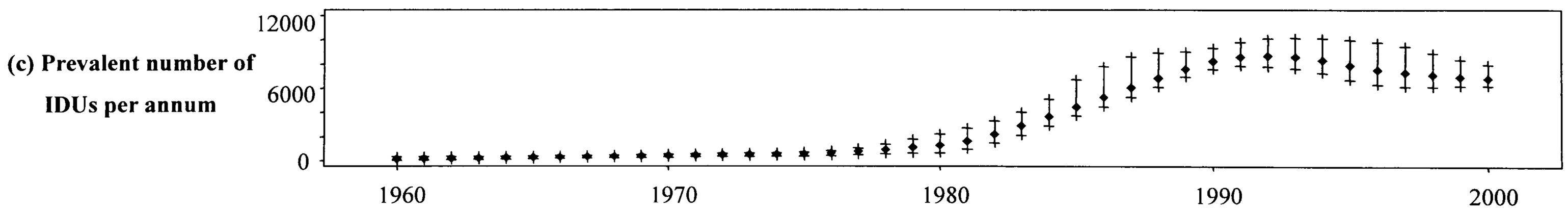
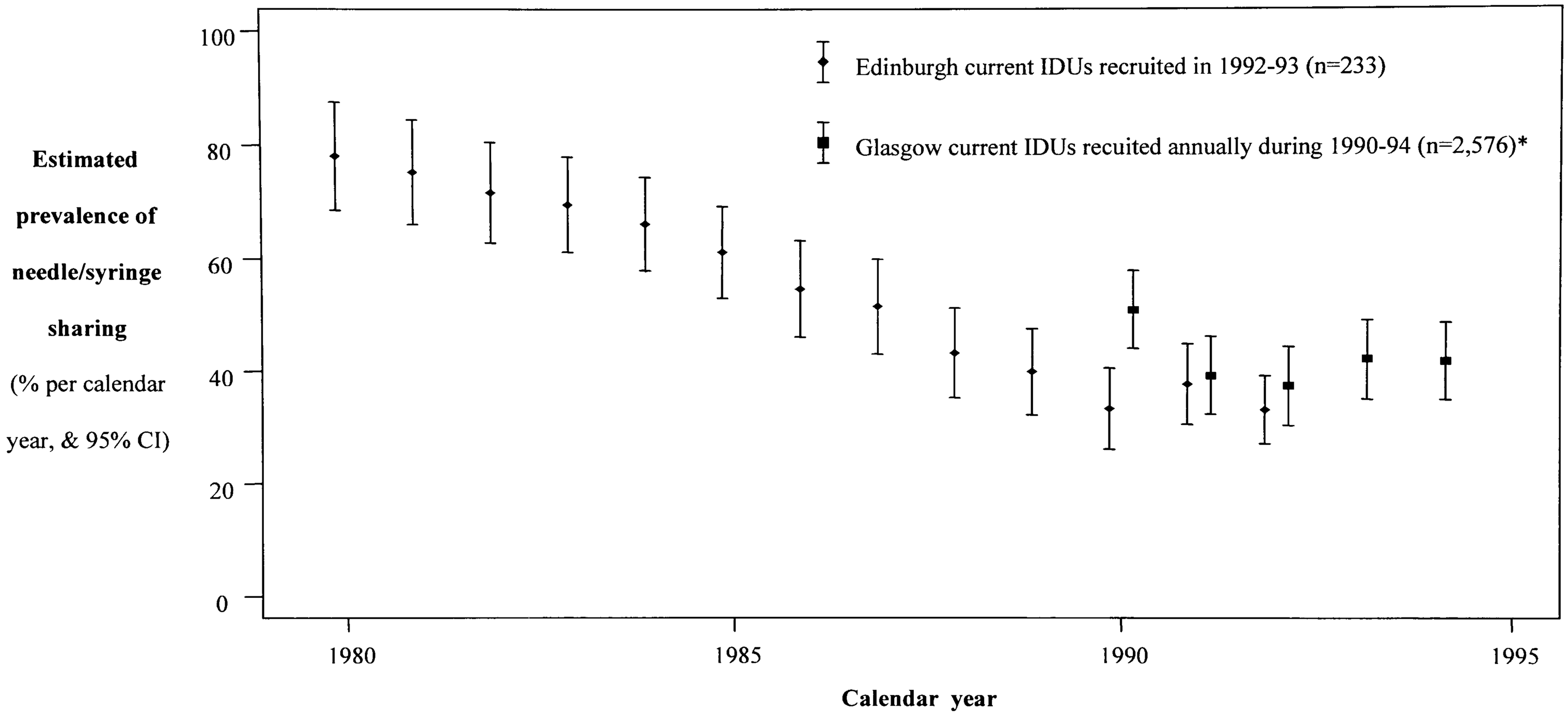


Figure 3.2: Prevalence of needle/syringe sharing reported by IDUs recruited in Glasgow and Edinburgh surveys.



* Prevalences of needle/syringe sharing reported during previous 6 months were adjusted to 12 months, by applying a factor of 14% derived from data obtained in the 1999 survey (i.e. among a restricted sample of Glasgow IDUs who had commenced injecting since 1990, 36% reported needle/syringe sharing in the previous 6 months and 14% of those who had not shared in the previous 6 months had shared in the 6 months before that).

Figure 3.3: Graph showing the number of partners with whom IDUs in Glasgow, recruited during community-wide surveys in 1990-1994, reported needle/syringe sharing (i.e. injected at least once with their used needle/syringe) during the previous six months and the geometric distributions used in the model to approximate these data.

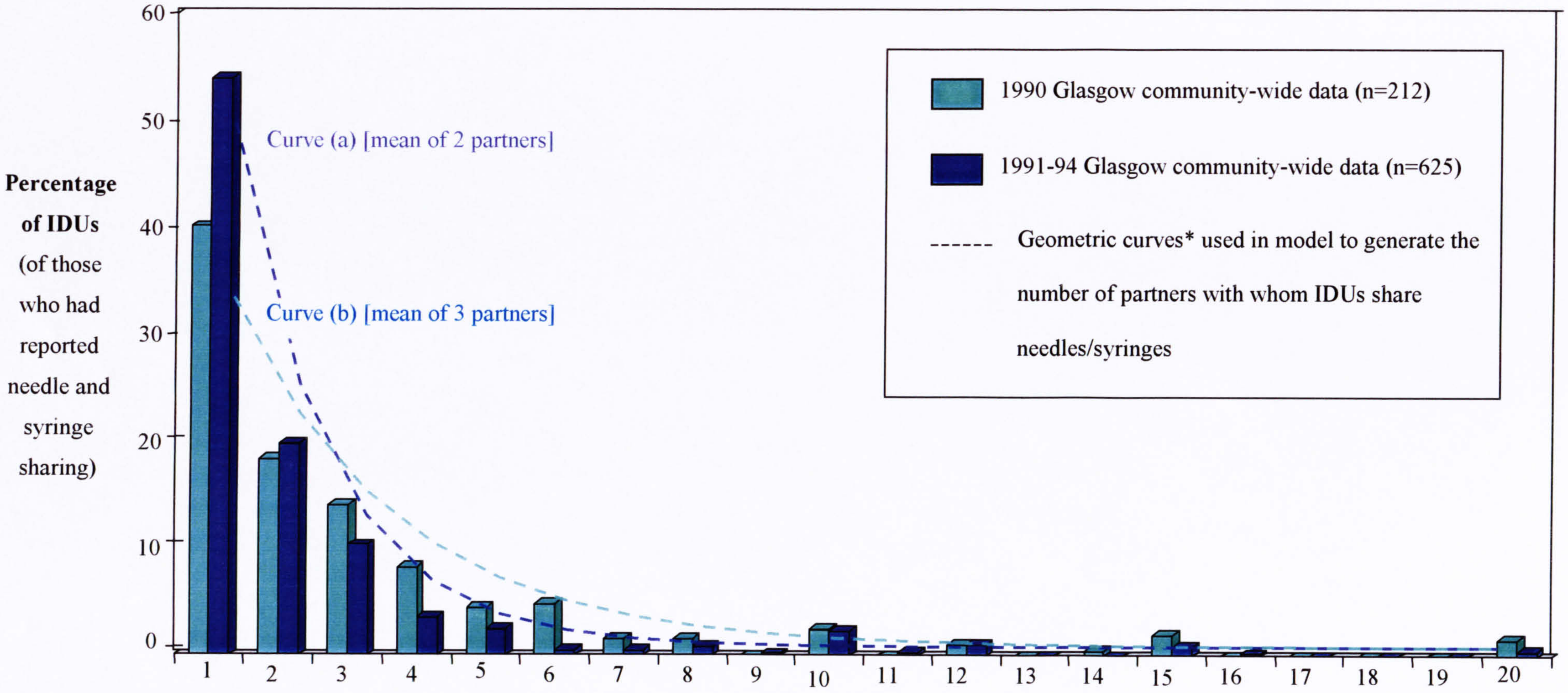


Figure 3.4: Barplot showing the percentage of injecting episodes where a needle/syringe was shared among 837 Glasgow IDUs recruited during surveys conducted in 1990 and 1991-94, stratified by whether respondents reported having either (a) 1, (b) 2-5, (c) 6-10, or (d) 11-20 sharing partners during the previous six months.

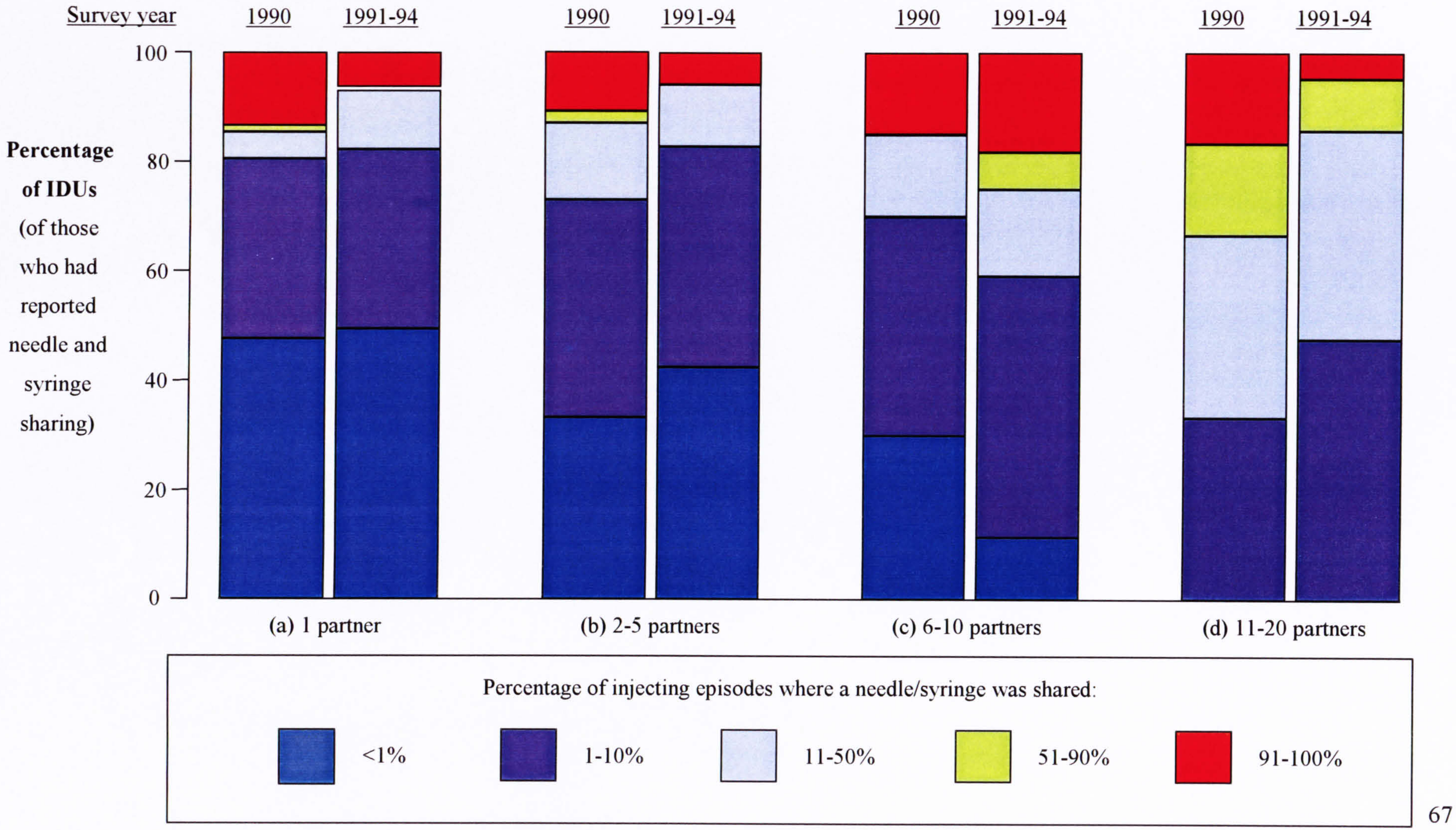
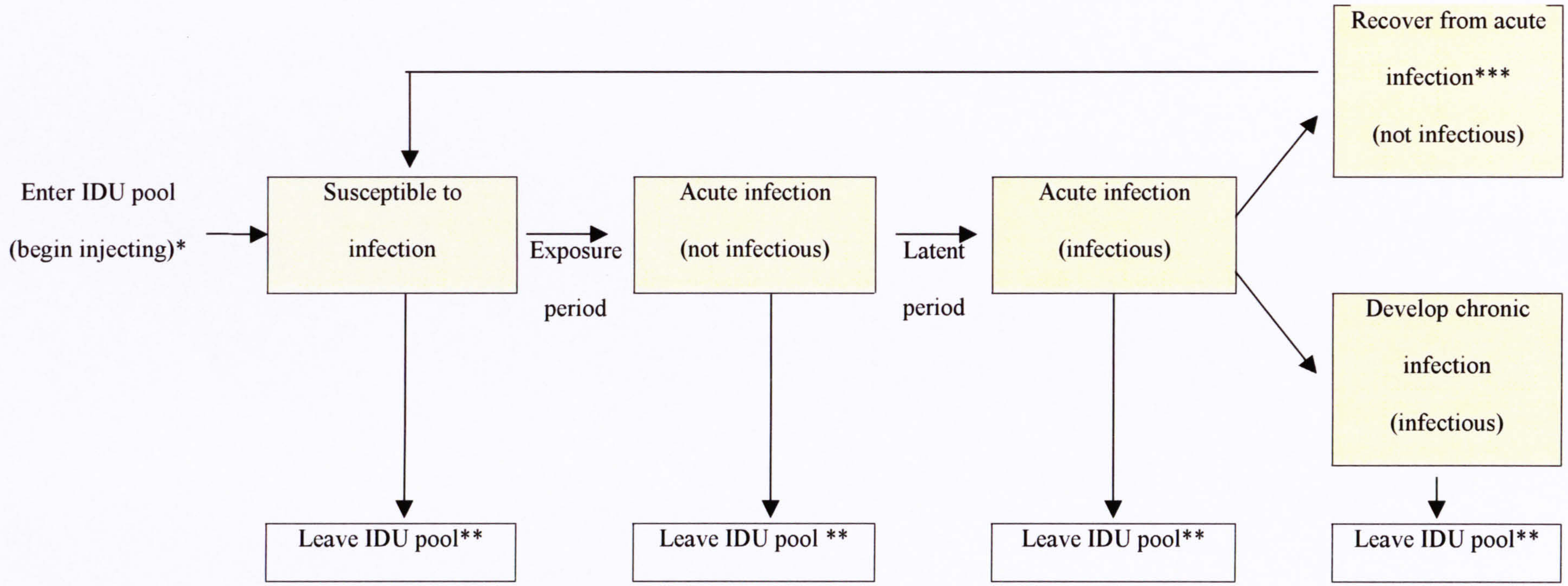


Figure 3.5: States of HCV infection followed by individuals commencing injecting drug use.



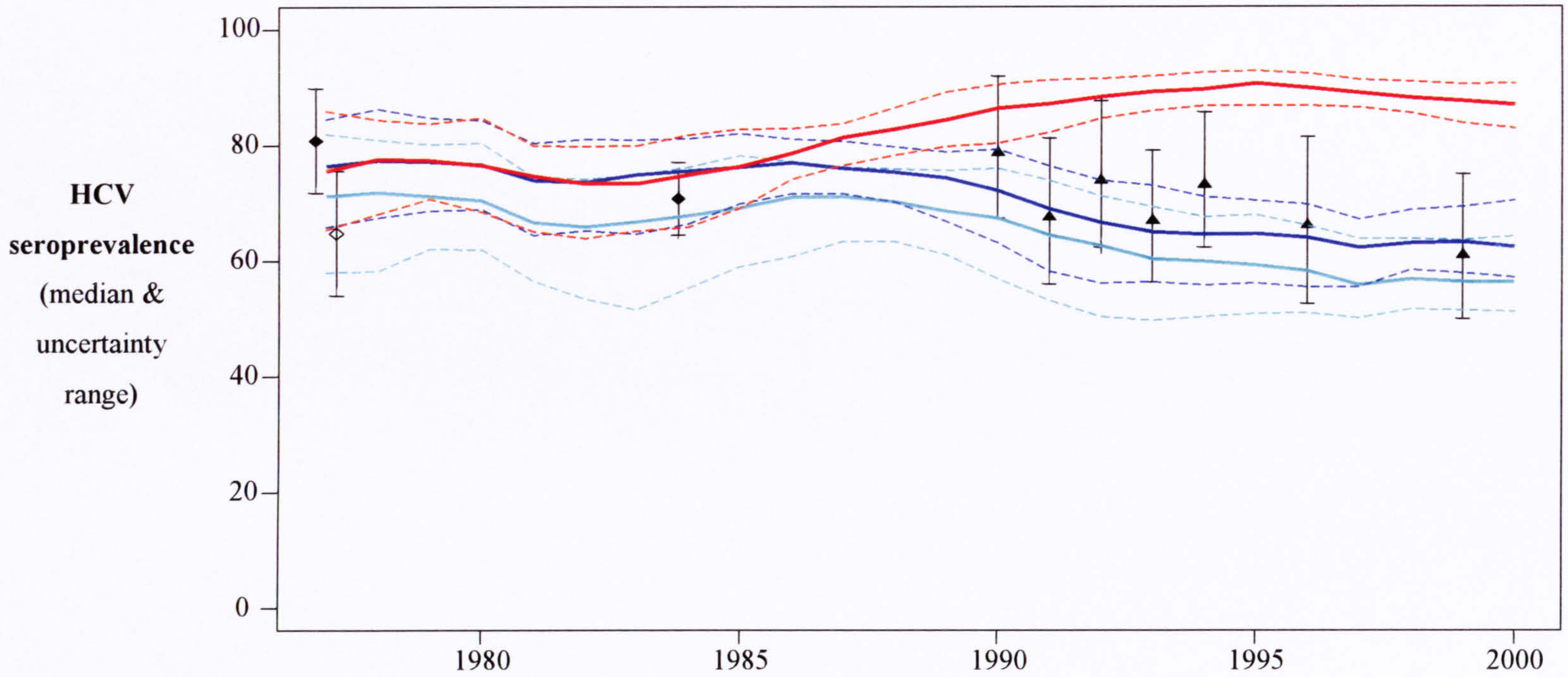
Infection states followed in the IDU pool.

* Individuals entering the injector pool for the first time are susceptible to infection; in order to initiate the spread of the virus, a small number of the established pool of IDUs were randomly assigned carrier status.

** Individuals leave the injector pool from either permanently stopping injecting or death.

*** For HCV, 15-40% of individuals clear their virus following acute HCV infection; these individuals re-enter the susceptible group (see Methods).

Figure 3.6: Modelled and observed seroprevalences for HCV among current IDUs in Glasgow, 1975-2000.



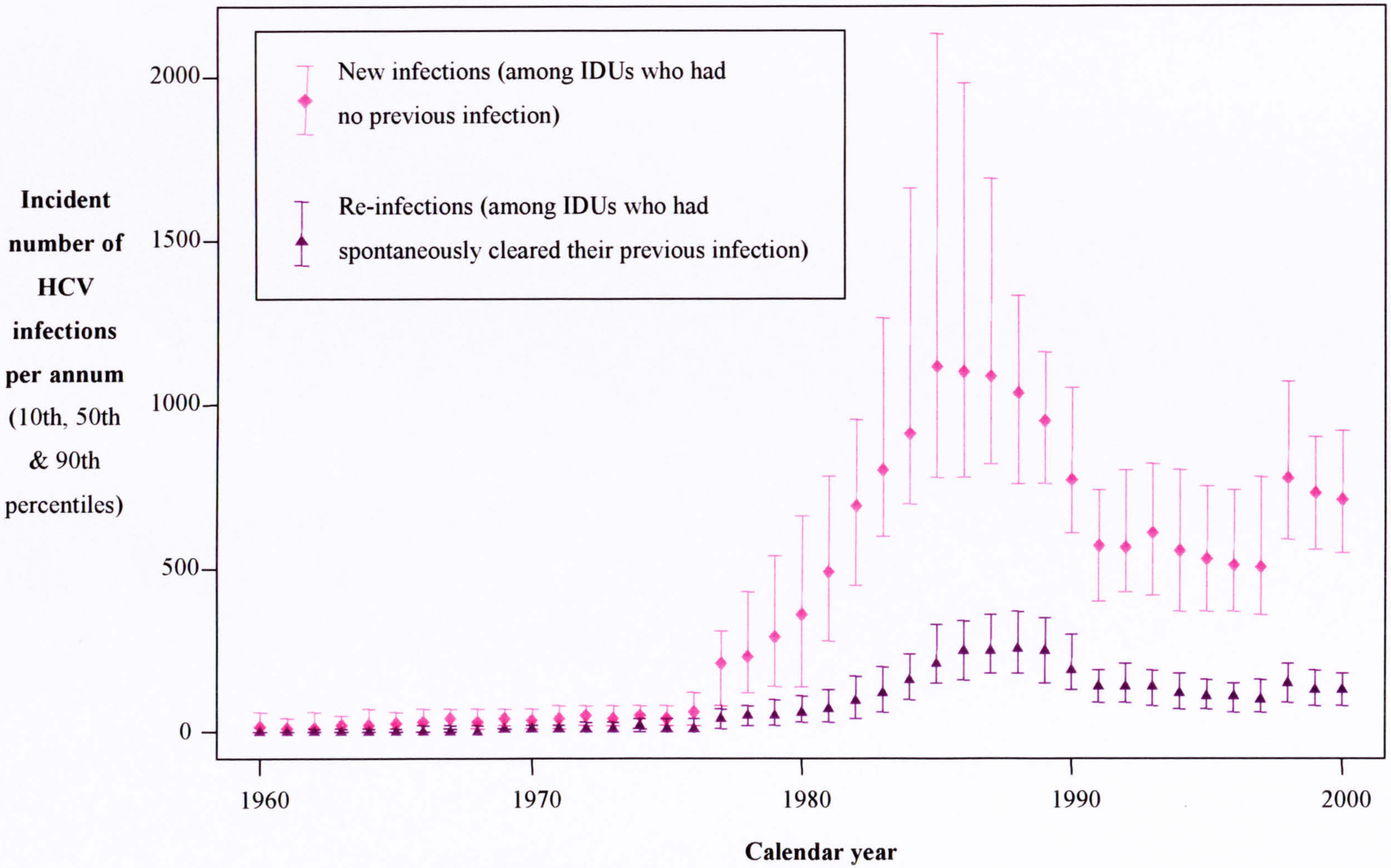
Observed HCV seroprevalences & 95% CIs:

- Community-wide surveys;
- UAT of samples originally tested HBV sAg positive & negative, respectively;

Modelled HCV seroprevalences (10th, 50th and 90th percentiles) from three approaches:

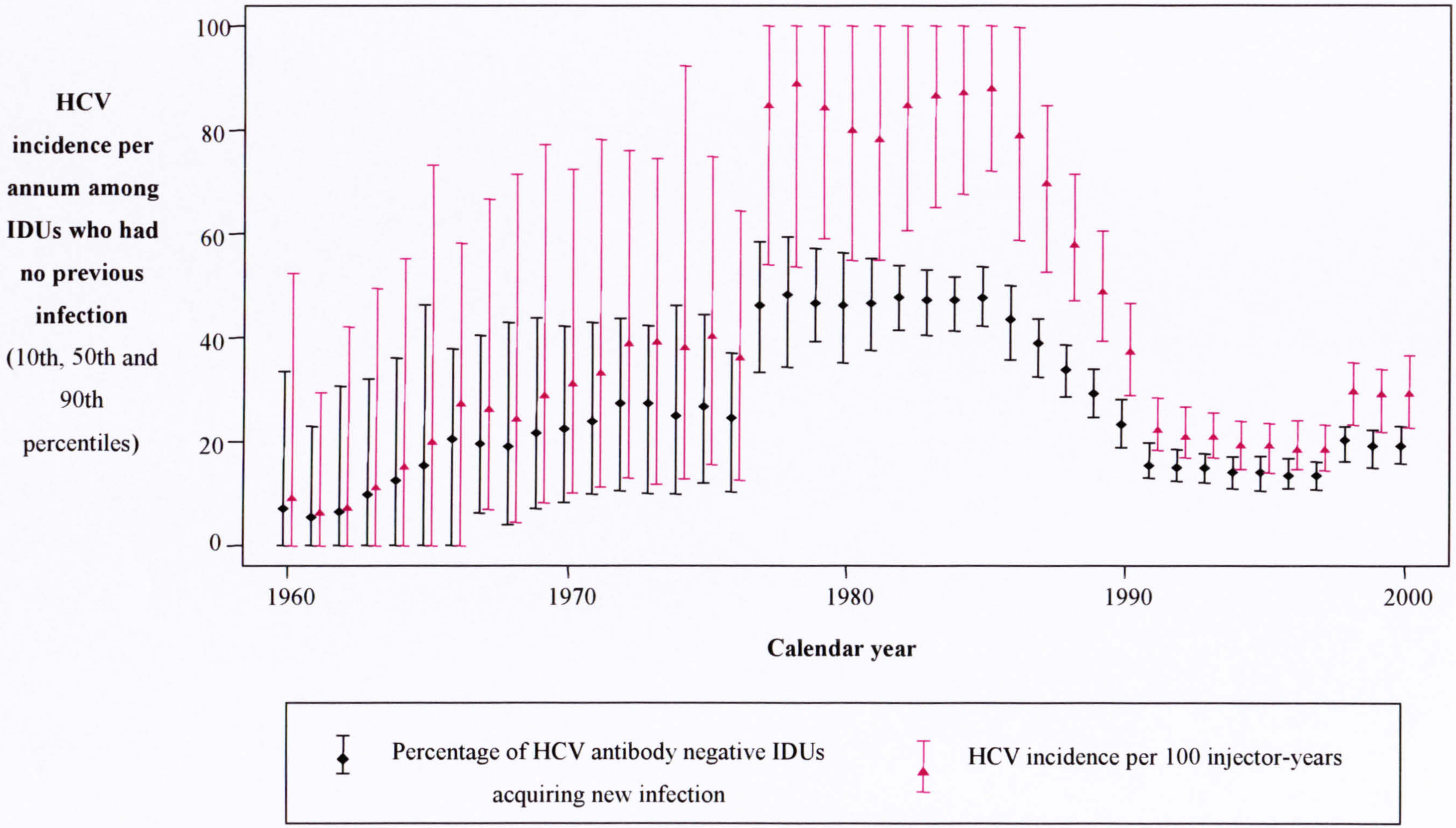
- (a) Model with higher infectivity employed during the short period of high viraemia following seroconversion;
- (b) Model without higher infectivity employed during the short period of high viraemia following seroconversion;
- (c) Model with high needle/syringe sharing rates from early to mid 1980s carried forward to 1988-2000.

Figure 3.7: Modelled incident number of HCV infections per annum among current IDUs in Glasgow, 1960-2000*.



* Data generated by model (a) which employed higher infectivity to newly HCV infected IDUs during the short period of high viraemia following seroconversion.

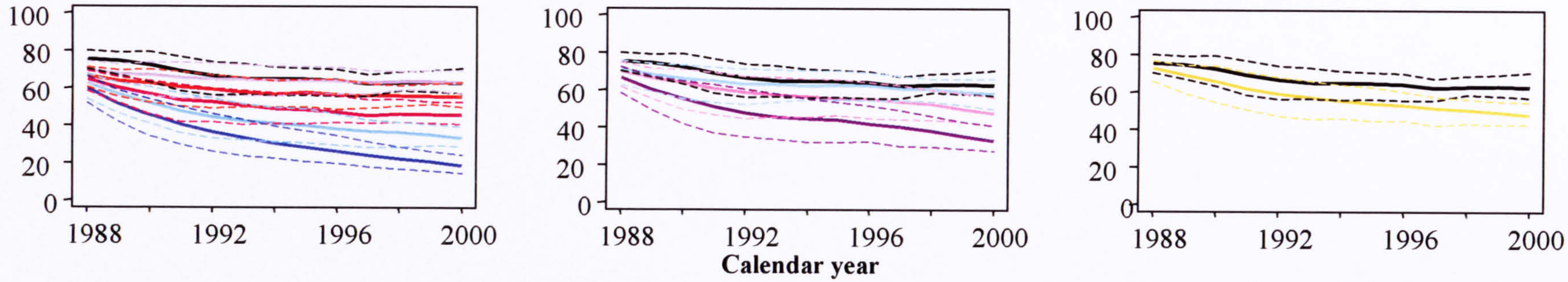
Figure 3.8: Modelled HCV incidence per annum among HCV antibody negative IDUs in Glasgow, 1960-2000*.



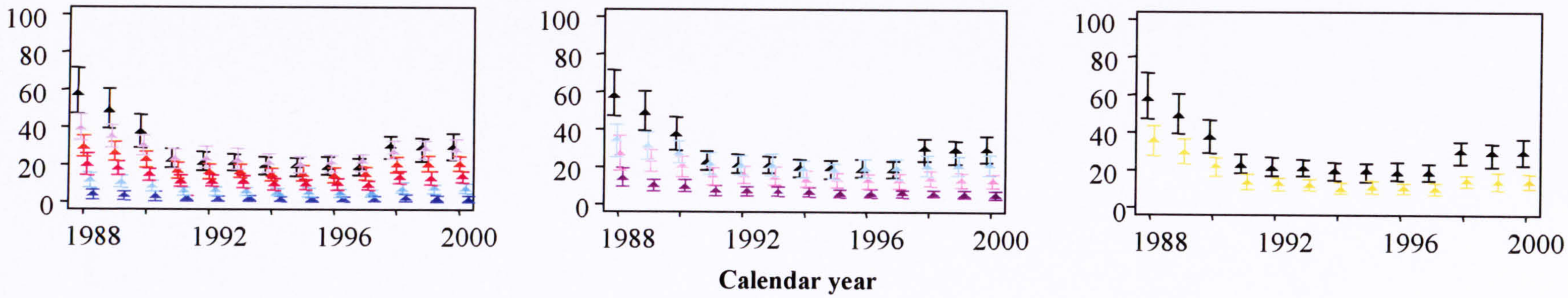
* Data generated by model (a) which employed higher infectivity to newly HCV infected IDUs during the short period of high viraemia following seroconversion.

Figure 3.9: Modelled impact of hypothetical lower risk behaviours – in terms of (i) the percentage of IDUs who had shared a needle/syringe per year, (ii) the mean number of needle/syringe sharing partners per year, and (iii) the percentage of injecting episodes shared – on (a) HCV seroprevalence and (b) HCV incidence among current IDUs in Glasgow, 1988-2000.

(a) Modelled HCV seroprevalence (10th, 50th and 90th percentiles)



(b) Modelled HCV incidence per 100 injector-years among IDUs who had no previous infection (10th, 50th and 90th percentiles)



(i) The percentage of IDUs who had shared a needle/syringe per year:

- 45-79%, 35-49% and 40-54% during 1988-90, 1991-97 and 1998-2000, respectively;
- 41-50% during 1998-2000;
- 31-40% during 1998-2000;
- 21-30% during 1998-2000;
- 11-20% during 1998-2000;
- 1-10% during 1998-2000.

(ii) The mean number of needle/syringe sharing partners per year:

- 3-6, 2 and 3 during 1988-90, 1991-97 and 1998-2000, respectively;
- 2.0 during 1998-2000;
- 1.5 during 1998-2000;
- 1.0 during 1998-2000.

(iii) The percentage of injecting episodes where a needle/syringe was shared:

- As illustrated in Figure 3.4;
- Limited to <10% .

3.5 Appendix

3.5.1 Generating the number of needle/syringe sharing partners per year

The following expression was applied:

$$x_{i,k} = \begin{cases} G(1/p_k) + 1 & \text{for } i = 1,\ldots,s_k; \quad \text{where } k=1960, \ldots, 2000; \\ 0 & \text{for } i = s_{k+1},\ldots,n_k; \text{ where } k=1960, \ldots, 2000; \end{cases}$$

to generate a vector, $x_{i,k}$, of the number of partners to assign to n_k IDUs, in a given year k, where s_k was the number of the n_k IDUs who had been determined to share needle/syringes on at least one occasion during year k, and $G(1/p_k)$ were non-negative integers randomly generated from the geometric distribution with probability $1/p_k$, where p_k was the mean number of partners for year k.

3.5.2 Weighting the probability of assigning a number of needle/syringe sharing partners to each IDU per annum according to the number of partners assigned in the previous year

The following expression was used to weight the probability of selecting each element of $x_{i,k}$ for the jth person in the pool of n_k IDUs:

$$w_{i,j,k} = 1/(|x_{i,k} - y_{j,k-1}|+1)^2 \qquad \text{for } i=1,\ldots,n_k \text{ and } j=1,\ldots,n_k; \text{ where } k=1960,\ldots,2000;$$

where $x_{i,k}$ represents the number of partners to assign to each person in the pool of n_k IDUs for year k and $y_{j,k-1}$ represents the number of partners the jth IDU had been assigned in the previous year.

As a simplified example: for a given year, say 1990, in a pool of four IDUs (i.e. $n = 4$), where the first IDU had been assigned zero partners in the previous year (i.e. $y_{1,1989} = 0$), if a vector $x_{i,1990}=(0,0,2,20)$ (i.e. $x_{1,1990}=0$, $x_{2,1990}=0$, $x_{3,1990}=2$, *and* $x_{4,1990}=20$) had been generated for the number of partners to assign to these four IDUs

in 1990, then the weights associated with the first IDU selecting elements of $x_{i,1990}$ would be:

$$w_{1,1,1990} = 1/(|0-0|+1)^2 = 1;\ w_{2,1,1990} = 1/(|0-0|+1)^2 = 1;$$

$$w_{3,1,1990} = 1/(|2-0|+1)^2 = 1/9;\ w_{4,1,1990} = 1/(|20-0|+1)^2 = 1/441.$$

Normalizing these weights (1, 1, 1/9, 1/441) produces a vector of probabilities (0.473, 0.473, 0.052, 0.001) associated with the first IDU selecting elements of $x_{i,1990}$; under random selection, the vector of selection probabilities would have been (0.25, 0.25, 0.25, 0.25). If we assume that $x_{1,1990}$ was assigned to the first IDU under weighted selection, this selection process would continue for the second IDU *without* replacing the chosen number of partners in the vector (i.e. $x_{i,1990}$ would reduce to (0,2,20)).

The following expression was calculated at the start of each year to compare the average change in the number of partners assigned to IDUs between random and weighted selection:

$$z_k = \frac{\sum_{j=1}^{n_k} | y_{j,k-1} - y_{j,k} |}{n_k} \text{ for } j=1,\ldots,n_k;\ \textit{where } k=1961,\ldots,2000;$$

where $y_{j,k-1}$ and $y_{j,k}$ represent the number of partners the jth IDU, from a total of n_k IDUs, had been assigned in years k-1 and k.

3.5.3 Weighting the probability of selecting actual needle/syringe sharing partners for each IDU per year according to the number of partners each IDU has been assigned

The expression $1/(|x_{i,k}-x_{j,k}|+1)^2$ was applied to weight the probability of the j^{th} IDU selecting as a partner the i^{th} IDU of the remaining pool of sharing individuals where $x_{j,k}$ and $x_{i,k}$ represent the number of partners assigned to these respective individuals in a given year k.

3.5.4 Viral factors used in HIV transmission model

Further, to validate the model findings, the transmission of HIV infection was also simulated among the current IDUs in Glasgow by applying the same population and behavioural factors as described in Sections 3.2.2.1 and 3.2.2.2, respectively, and accommodating the following viral characteristics:

(i) The first case of HIV among Glasgow IDUs was introduced in 1983[165];

(ii) Individuals were only exposed to HIV through the sharing of needles/syringes. Sexual transmission of HIV is more common than HCV, however needle/syringe sharing is generally regarded as the most important means of spread between IDUs[141,151];

(iii) The transmission probability for HIV was assumed to be ten times lower (i.e. mean 0.3%) than that of HCV[129,160]. A short period (6-8 weeks) of high viraemia[139,142] follows infection with HIV, and has been related to increased infectivity[140]. It was therefore assumed that infectiousness increased 10-fold during this initial high viraemia phase[151,141];

(iv) The latency period for HIV was taken to be 50 days[166];

(v) All individuals who acquired HIV developed chronic infection and remained infectious[129].

Chapter 4: Severe disease burden associated with hepatitis C virus infection in Scotland, 1991-2001: record-linkage study

4.1 Background

Progression to severe sequelae of hepatitis C virus (HCV) infection, namely hepatocellular carcinoma (HCC) and decompensated cirrhosis, generally takes several decades and varies according to age, gender, alcohol consumption and co-infection with other blood-borne viruses[5]. An epidemic of severe liver disease has been predicted in Australia and the United States as a consequence of the large numbers of people who became infected with HCV through injecting drug use in the 1970s and 1980s[81,83,167]. To monitor the emergence of such a problem requires national surveillance systems, currently lacking in the UK and elsewhere, which detect not only advanced liver disease but also the aetiological factors.

Numerous studies have examined national trends in HCC but few have provided data on the underlying cause. The increasing burden of HCV infection is a likely explanation for the rise in HCC incidence over the past two to three decades reported in Japan[168], North America[169,170], Australia[171] and parts of Europe[172,173]. Alcohol was discounted as the predominant risk factor, except in Japan[174], because of declining rates in consumption[169,170,171,172,173]. One study, confined to US veterans, deduced HCV from medical history records to be the most important underlying cause for the increase in hospitalisation for primary liver cancer[175]. In 80 patients presenting to a Scottish hospital, who had available stored serum samples, HCV infection was identified as a major risk factor for the development of HCC[39]. Moreover, the age-specific incidence of HCC has progressively shifted toward younger people[169].

It has also been suggested that HCV has played a role in the rise in alcohol related deaths, mostly due to liver damage, in England between 1983 and 1999[176]. Disproportionately high prevalences of HCV infection have been found in alcoholic patients with liver disease (43% from two studies with 61[177] and 40[178] patients), compared to those without liver disease (2% (1/45)[177] and 10% (6/60)[178], respectively). Further, the prognosis among patients with high alcohol consumption and HCV antibodies was significantly worse than for those without HCV antibodies[179,180,181]. Among patients hospitalised in Japan with liver cirrhosis, a considerably higher percentage of those with both HCV and alcohol present had developed HCC (51%, 151/297) compared to those with only one of these two risk factors (HCV-alone: 37%, 156/420; alcohol-alone: 17%, 20/119)[182]. In direct contrast, a recent study of 213 patients reported that survival in alcoholic cirrhosis patients was not influenced by the presence (72) or absence (141) of HCV infection[183]. This apparent discrepancy may have been due to confounding factors[184]. Determining the extent to which alcohol and other factors, such as HIV, influence the course of HCV epidemics will inform (i) the development of appropriate interventions and (ii) models to forecast the future burden of severe disease.

There is thus an urgent need in Scotland and elsewhere[185] to provide accurate, up-to-date information about the current burden of HCV-related severe disease to help policymakers prioritise health interventions and allocate resources accordingly. To improve our understanding of the epidemiology of HCV infection in Scotland, a nationwide surveillance system was established to collect laboratory data on all persons diagnosed HCV antibody positive[186]. The existence of this and other high-quality national computerised databases on hospital discharges, cancer registrations

and deaths[187] afforded an opportunity to adopt a record-linkage approach to examine the occurrence of liver failure and cancer associated with HCV infection in Scotland.

4.2 Aims

The aims of the work presented in this chapter were to:

(i) estimate the annual number of new diagnoses for decompensated cirrhosis and HCC related to HCV infection in Scotland;

(ii) examine the epidemiological characteristics, in particular the presence of alcohol and HIV infection, of HCV-related decompensated cirrhosis and HCC cases in Scotland;

(iii) determine the influence of epidemiological risk factors on the development of decompensated cirrhosis and HCC among HCV diagnosed persons in Scotland;

(iv) determine the mortality rate following hospitalisation with decompensated cirrhosis and HCC among HCV diagnosed cases in Scotland;

(v) estimate the prevalence of diagnosed HCV infection among all decompensated cirrhosis and HCC cases in Scotland.

Estimates of (i) were also produced for Greater Glasgow to allow validation of the model, in Chapter 6, designed to estimate and project the burden of HCV-related disease among IDUs in this area. Data from (ii), (iii) and (iv) provide a Scottish perspective on the natural history of HCV infection. Data from (v) will provide an understanding of the contribution of HCV in the rising incidence of severe liver disease reported in the UK and in other developed countries.

4.3 Methods

4.3.1 Design overview

Scotland's database of HCV diagnosed persons was linked with other nationally held databases on hospital admissions, cancer registrations and deaths to determine HCV diagnosed patients' development of, and mortality from, severe sequelae (namely HCC and decompensated cirrhosis) during 1991-2001. Not all instances of the above severe disease outcomes related to HCV infection would be detected through this approach – for example, due to undiagnosed HCV infection – and thus hospital data were adjusted to account for this (described below). Data on epidemiological risk factors – in particular excessive alcohol use and coinfection with HIV – acquired through the record-linkage process, were assessed in relation to the development of decompensated cirrhosis and HCC. The mortality rate following hospitalisation with HCV-related decompensated cirrhosis and HCC cases in Scotland was also determined. Finally, the numbers of new hospitalisations and deaths from HCC and decompensated cirrhosis related to diagnosed HCV infection were compared with all new hospitalisations and deaths from these causes (i.e. regardless of HCV status) in Scotland during 1996-2001 to estimate the prevalence of diagnosed HCV infection in end-stage liver disease.

4.3.2 Study population

The study population comprised all persons who had been diagnosed HCV antibody positive in Scotland up to the 31st December 2001. Epidemiological data on laboratory reported HCV diagnoses are held at the Scottish Centre for Infection and Environmental Health (SCIEH)[186]; laboratory under-reporting is not an issue because diagnoses are confirmed by virology laboratories in which dedicated surveillance staff

collate and forward the data to SCIEH. The database consists of cases who were diagnosed since testing first began in 1991 and a minority (<1%) who were retrospectively tested HCV antibody positive prior to this. Data collected include date of the earliest positive specimen, source of specimen (e.g. hospital, general practice, genito-urinary medicine clinic, prison), risk information and a limited set of personal identifiers ((a) forename initial, (b) surname initial, (c) surname soundex[188], (d) date of birth, (e) gender and (f) postcode district of residence at diagnosis) to eliminate repeat tests; full names are not held to preserve patient confidentiality[188]. Records are updated (but, regrettably, date of updating is not registered) if missing data on risk or other relevant epidemiological information become available from subsequent tests. At the end of December 2001, records from 13,519 persons in Scotland diagnosed with HCV were held on the database[189].

4.3.3 Data sources used to identify information on disease outcomes and other epidemiological risk factors

4.3.3.1 Scotland's hospital discharge, cancer and deaths databases

The Information and Statistics Division (ISD) in Edinburgh holds national computerised data on (i) hospital (general acute inpatient and day case) discharge records for non-psychiatric, non-obstetric specialties[190], (ii) cancer registrations[190] and (iii) Registrar General's death records[191]. Diagnoses pertinent to either the patient's hospital stay, cancer registration or cause of death were coded according to the International Classification of Diseases (ICD) Ninth[192] (in years 1980-1995 for hospital discharges and 1980-1999 for deaths records) and Tenth Revisions[193] (in years 1996-2001 for hospital discharges, 1980-1998 for cancer and 2000-2001 for deaths records; data were only available up to 1998 for cancer registrations and

therefore were merely used to assess the reliability of hospital discharge data). Records on these databases contained full identifying information, including the limited set of identifiers listed (a)-(f) above, required to link to the HCV diagnoses database. A measure of a patient's deprivation status was also available with each record and had been derived from their postcode of residence based on the Carstairs and Morris index, which combines four census indicators (overcrowding, unemployment, social class and car ownership), judged to represent material disadvantage in the population, into a single composite seven-point score, ranging from very affluent (1) to very deprived (7), for each postcode sector in Scotland[194,195].

4.3.3.2 Scotland's HIV test database

SCIEH holds epidemiological non-named data on all persons who have had a personal HIV antibody test in Scotland since 1989[196]. These data are collected through the use of a national HIV test request form, which accompanies the blood specimen sent for HIV testing to the appropriate laboratory[197]. Data retained at SCIEH include date of specimen, HIV antibody test result, risk category associated with HIV test and identifiers (a)-(f) listed above.

4.3.4 Record-linkage process

The HCV diagnoses database was linked to (i) hospital discharge records, (ii) cancer registrations and (iii) death records by ISD's Record Linkage Team using a previously developed probability matching approach[187]. The identifier fields used in the linkage process were as listed (a)-(f) above. ISD have estimated that both the false negative rate (the proportion of truly matched pairs which the system fails to link) and the false positive rate (the proportion of linked pairs of records which do not refer to the same

individual) with this approach to be less than 5%[187], similar to that found recently in an independent assessment of matching using non-name-based case registries[198]. ISD also performed an internal linkage of records on the HCV diagnoses database to identify any overlooked duplicate cases (see Results). These linkages were approved by the Privacy Advisory Committee, which oversees issues of confidentiality involving data on National Health Service patients in Scotland. Once these linkages were completed, ISD provided SJH with data from the hospital, cancer and deaths registries on HCV diagnosed persons for subsequent analyses as described below.

To secure further data on the injecting and HIV positive status of HCV diagnoses, a linkage of the HCV diagnoses database with a subset of the HIV test database (on records of those who had indicated that they had injected drugs or who had tested HIV positive) was performed by SJH. The surname soundex of HIV tested persons was incomplete and thus excluded from the linkage process. Individuals who matched exactly on forename initial, surname initial, date of birth and gender were assumed to be the same person; the sensitivity and specificity of matching based only on these identifiers was assumed to be in excess of 95%[198].

4.3.5 Definition of disease outcomes and other epidemiological risk factors

4.3.5.1 Hepatocellular carcinoma (HCC)

HCC was identified on the hospital discharge, cancer and deaths databases by a diagnosis of primary liver cancer (ICD-9 code 155.0; ICD-10 code C220). The cancer database was also able to identify those who had histologically confirmed HCC.

4.3.5.2 Decompensated cirrhosis

Decompensated cirrhosis was defined as ascites, oesophageal varices with bleeding, hepatic encephalopathy, chronic hepatic failure and alcoholic hepatic failure (identified as ICD-9 codes: 456.0, 571.3, 572.2, 572.8, 789.5; ICD-10 codes: I850, I982, K704, K709, K721, K729, R18).

4.3.5.3 Epidemiological risk factors

For each HCV diagnosed case, their linked hospital discharge and death records were searched for mention of alcohol (as defined by ICD-9 codes: 291, 303.9, 305.0, 571.0-571.3; ICD-10 codes: F10, K70), hepatitis B virus (HBV) (ICD-9 codes 070.2, 070.3; ICD-10 codes: B16, B170, B180, B181) and opiate dependence (ICD-9 codes: 304.0, 304.7; ICD-10 codes: F11). A second variable for alcohol abuse (as defined by ICD-9 codes: 291, 303.9, 305.0; ICD-10 codes: F10) was also created which excluded alcoholic liver disease. Data on opiate use (from a hospital admission or death record) and injecting drug use (with a HIV test) were used to establish the IDU risk status of HCV diagnosed persons for whom no risk factor information were available. The maximum Carstairs and Morris deprivation score recorded in patients' linked hospital discharge and death records was used to establish if HCV diagnosed persons had resided in an area of high deprivation (represented by scores 6 and 7).

4.3.6 Analyses

4.3.6.1 Characteristics of HCV diagnosed persons

A comparison of HCV diagnoses' characteristics (i.e. year and age at diagnosis, gender, risk group, health-board of residence, referral source) was made between those who had sufficient and insufficient identifiers for linkage with other databases;

insufficient identifiers amounted to absence of date of birth or both forename and surname initials. Uni-factorial and multi-factorial logistic regression were used to determine the factors significantly associated with non-linkage of HCV diagnosed cases.

4.3.6.2 Epidemiological risk factors of HCV diagnosed persons

The HIV diagnosis, deprivation, alcohol and HBV status of HCV diagnosed persons were obtained from examining their HIV test, hospital discharge and death records. The IDU status of HCV diagnosed persons was sourced from four databases (i.e. HCV diagnoses, HIV test, hospital discharge and death databases; data on opiate use, instead of IDU, was only available from the latter two databases). Log-linear modelling[199] was then used to analyse the overlaps in the number of HCV diagnosed IDUs among the four data-sources and estimate the total (including hidden) number of HCV diagnosed IDUs. Stepwise regression was used to find a model which adequately described the data with as few parameters as possible; retention of interaction terms was further assessed by comparison of the residual deviance with the χ^2 distribution.

4.3.6.3 Characteristics of HCC and decompensated cirrhosis cases among HCV diagnosed persons

The epidemiological characteristics of new diagnoses (first hospital admissions) and deaths (both underlying and all causes) from HCC and decompensated cirrhosis during 1991-2001 were examined. In particular, the proportion of deceased cases with each condition (i.e. HCC and decompensated cirrhosis) who had also been hospitalised with this condition was determined (for purposes of adjusting observed

data, as described below). Additionally for HCC, the proportions of hospitalised and deceased cases who had been registered on the cancer database (complete to 1998) were also determined.

4.3.6.4 Annual numbers of new diagnoses for HCC and decompensated cirrhosis related to HCV infection

The annual number of first hospital admissions for HCC and decompensated cirrhosis among individuals who were already HCV diagnosed prior to hospitalisation or within 14 days were adjusted to account for (i) the inability to link a proportion of HCV diagnosed cases due to insufficient identifiers, (ii) the non-hospitalisation of HCC and decompensated cirrhosis cases (estimated from the proportion of deaths not previously hospitalised for these conditions), and (iii) the non-diagnosis of HCV infection among HCC and decompensated cirrhosis cases (estimated from the proportion of those hospitalised for decompensated cirrhosis who were not diagnosed with HCV infection until >14 days after their hospitalisation); details given in footnote to Table 4.6. No adjustment was made for the high sensitivity and specificity of the record-linkage process. Adjusted annual diagnoses for HCC and decompensated cirrhosis were restricted to the period 1996-2001, due to limited HCV testing prior to this period.

4.3.6.5 Risk factors for development of HCC and decompensated cirrhosis among HCV diagnosed persons

Cox proportional hazards regression[200] was used to assess the influence of epidemiological factors on the development of outcomes (i) HCC and (ii) decompensated cirrhosis among diagnosed HCV positive persons in Scotland. The

period of observation used in calculating the risk of either outcome began at the date of first HCV positive specimen and ended at the date of hospitalisation for the relevant outcome (either HCC or decompensated cirrhosis), date of death, or the end of December 2001, whichever came first. Covariates examined included baseline characteristics at the time of HCV diagnosis (i.e. gender, risk group, health-board of residence and referral source) and time-dependent covariates (i.e. current age, first hospitalisation for alcohol abuse and HBV, and diagnosed HIV infection). Analysis was confined to persons who were outcome free at the start of follow-up and thus cases who were admitted to hospital for the relevant condition (i.e. HCC or decompensated cirrhosis) prior to or within 14 days of HCV diagnosis were excluded; furthermore, those who had been retrospectively diagnosed with HCV and had their first positive test result prior to 1991 were also excluded from analyses. Models were assessed for HCV diagnosed cases referred from all settings and separately on cases referred only from non-hospital settings. In an additional analysis, the risk period was defined in terms of age (i.e. from age at first HCV positive specimen to age at end of follow-up) to examine the influence of other characteristics on the development of decompensated cirrhosis as age advances.

4.3.6.6 Mortality related to HCC and decompensated cirrhosis among HCV diagnosed persons

Following first hospitalisation for HCC, the number of deaths from all causes and from HCC (given as the underlying cause or contributing cause with the underlying cause stated as liver or HCV related) and the number of cases who had been in hospital for a liver transplant (ICD-9 code: V42.7; ICD-10 codes: Z94.4), according to gender and age at time of hospitalisation for HCC, were determined. The person-years

at risk were calculated as time in years from date of first hospitalisation for HCC to date of death, date of liver transplant or the end of December 2001, whichever came first; cases who had either (i) died on the same day as or (ii) received a liver transplant prior to first admission with HCC were excluded (i.e. for HCC: (i) 0 and (ii) 2 cases excluded; also for decompensated cirrhosis: (i) 2 and (ii) 5 cases excluded). Cox proportional hazards regression was used to assess the influence of gender and age on mortality from (i) HCC and (ii) all causes following first hospitalisation with HCC; the probability of death from (i) and (ii) at one and two years since first hospitalisation with HCC were also estimated. The number of deaths, liver transplants, person-years and mortality associated with cases hospitalised for decompensated cirrhosis were similarly assessed.

4.3.6.7 Prevalence of diagnosed HCV infection among all HCC and decompensated cirrhosis cases in Scotland

Data on all first hospital admissions and deaths associated with HCC and decompensated cirrhosis in Scotland during 1996-2001 by gender, age, history of alcohol abuse and HCV diagnoses status (sourced from hospital discharge records, death records and linkage with SCIEH's HCV diagnoses database) were examined. Decompensated cirrhosis was defined as above (ascites, oesophageal varices with bleeding, hepatic encephalopathy, chronic hepatic failure and alcoholic hepatic failure) except that cases without mention of liver disease (ICD-9 codes 570-573; ICD-10 codes: K70-K77) or hepatitis (ICD-9 codes 070; ICD-10 codes: B16-B18) were excluded, to discount non-liver-related conditions associated with ascites and oesophageal varices, from this analyses.

4.4 Results

4.4.1 Characteristics of HCV diagnosed persons

Of the 13,535 entries on the HCV diagnoses database as at the end of 2001, 164 (1.2%) were recognised as duplicate records based on probability matching methods carried out by ISD. A further 1,275 (9.5%) of the remaining 13,371 records on the database either had date of birth (277) and/or both forename and surname initials (1,034) identifiers missing so that linkage was inhibited.

Table 4.1 shows the characteristics of the 12,096 HCV diagnosed cases who had sufficient identifiers for record-linkage compared with those of the remaining 1,275 cases who had insufficient identifiers and were not linked. The majority of all diagnosed cases were first tested positive in 1998-2001 (56%), male (69%), aged 20-34 years (63%), IDUs (90% of known risk cases) and 47% were referred from hospital settings. Referrals from GUM and drug/counselling clinics were significantly more likely than hospital referred patients to have insufficient identifiers for record-linkage (unadjusted odds ratios: 31.0 and 3.5; 95% CI 25.9-37.1 and 2.9-4.2, respectively). The completeness of identifier information varied by health-board of residence – highest in Lothian (94%), Tayside (93%), then Glasgow (91%) and lower in the rest of Scotland (88%). Persons diagnosed recently in years 1998-2001 (compared to pre 1994) and those aged 20-34 years (compared to 35 years and older) were significantly more likely to have insufficient identifiers recorded and thus were less represented in the subsequent record-linkage exercise.

Table 4.2(a) shows the characteristics of the 12,096 HCV diagnosed cases who had sufficient identifiers for record-linkage by risk group. Those who reported a non-IDU risk were more likely to have been diagnosed pre 1994 and resided outside Glasgow than either IDUs or not known risk groups. Those who reported IDU were

more likely to be male and younger than those belonging to non-IDU and not known risk groups. Finally those for whom a risk could not be ascribed were more likely than the reported IDUs and non-IDUs to have been referred from a hospital setting.

4.4.2 Epidemiological risk factors of HCV diagnosed persons

Of the 12,096 HCV diagnosed cases, 17% and 6% had alcohol and HBV mentioned on either a hospital discharge or death record, respectively, and 3% were diagnosed HIV positive (Table 4.2). Over half of linked cases (5469/9813) had resided in an area of high deprivation (measured by Carstairs score 6-7).

Sixty-eight percent (8244/12096) of HCV diagnosed persons had IDU (or opiate use) mentioned with at least one of their (i) HCV diagnosis, (ii) HIV test, (iii) hospital discharge or (iv) death records (Table 4.3). Log-linear modelling estimated that there were a further 2,404 HCV diagnosed persons who had not been identified as IDUs from these four data-sources. The model yielded an overall estimate of 10,648 HCV diagnosed IDUs (95% CI 9,753-12,047), which represents 88% (95% CI 81-100%) of all 12,096 diagnosed cases. An additional analysis, which excluded persons who reported a non-IDU risk with their HCV diagnosis, provided a similar estimate of the total number of HCV diagnosed IDUs (10,578 (95% CI 9,682-11,978)).

4.4.3 Characteristics of HCC and decompensated cirrhosis cases among HCV diagnosed persons

During 1991-2001, 71 HCV diagnosed persons were hospitalised for the first time with HCC (Table 4.4), of whom 58 (82%) had also died during this period (43 from underlying cause HCC, 5 contributing cause HCC and 10 other causes). In total, 67 persons died with HCC as their underlying (59) or contributing cause (8), of whom 50

(75%) had been hospitalised with HCC previously (48 during 1991-2001 and 2 pre 1991) and 17 (25%) had not been identified as having been hospitalised with HCC (24% (14/59) and 38% (3/8) of deceased cases with HCC as underlying or only as contributing cause, respectively). Of the eight who had died with contributing cause HCC, five (63%) had liver disease or HCV as their underlying cause. For those who had been hospitalised or died with HCC during 1991-1998, 95% (40/42) and 91% (39/43), respectively, were registered with HCC on the cancer database; 24% (13/54) of HCC cases on the cancer database had not been hospitalised with this diagnosis.

During 1991-2001, 514 HCV diagnosed persons were hospitalised for the first time with decompensated cirrhosis, of whom 312 (61%) had also died during this period (65 and 98 from underlying and contributing cause decompensated cirrhosis, respectively, 27 HCC, 36 from other diseases of the liver, 15 HCV and 71 other causes). In total, 196 persons died with decompensated cirrhosis as their underlying (75) or contributing cause (121), of whom 168 (86%) had been hospitalised with decompensated cirrhosis previously (163 during 1991-2001 and 5 pre 1991) and 28 (14%) had not been identified as having been hospitalised with decompensated cirrhosis (9% (7/75) and 17% (21/121) of deceased cases with decompensated cirrhosis as underlying or only as contributing cause, respectively; of note, a high proportion (24%: 5/21) of the latter group had been diagnosed with HIV antibodies). Of the 121 who had died with contributing cause decompensated cirrhosis, 7 (6%) had HCC and 60 (50%) had liver disease or HCV as their underlying cause. A further 73 deaths with underlying cause liver disease or HCV and without either decompensated cirrhosis or HCC were identified during 1991-2001.

The majority of HCC (73%), and less so decompensated cirrhosis (52%), hospitalisations were among HCV diagnosed cases without a risk group. A higher

proportion of HCC than decompensated cirrhosis first hospitalisations were aged 50 years or more (82% vs 31%, respectively) and were male (85% vs 75%, respectively). Only 6% of HCV-related HCC hospitalisations were not diagnosed with HCV antibodies until after 14 days following first admission with HCC, compared to 17% (90/514) of HCV-related decompensated cirrhosis hospitalisations. Of these latter 90 cases, 55 (61%) were diagnosed with HCV within a year of their first hospital admission for decompensated cirrhosis and of the remaining 35, 31% were HCV diagnosed within 14 days of a subsequent hospital re-admission for decompensated cirrhosis. Further, 81% of the 90 cases had either alcoholic hepatic failure or ascites (but not hepatic encephalopathy, chronic hepatic failure or varices) recorded with their first hospitalisation for decompensated cirrhosis (compared to 58% (245/424) of those who were diagnosed with HCV before or within 14 days of their first decompensated cirrhosis hospitalisation).

Alcohol use was associated with 41% of HCC hospitalisations and deaths, and 71% of decompensated cirrhosis hospitalisations rising to 97% of deaths with underlying cause decompensated cirrhosis. HIV and HBV were associated with only a small proportion of HCC (0% and 9%, respectively) and decompensated cirrhosis (5% and 13%, respectively) hospitalisations.

4.4.4 Annual numbers of new diagnoses for HCC and decompensated cirrhosis related to HCV infection

Table 4.6 shows the estimated numbers of new diagnoses for HCC and decompensated cirrhosis related to HCV infection according to region (as described in footnote to Table 4.6, by accounting for (i) the inability to link a proportion of HCV diagnosed cases due to insufficient identifiers, (ii) the non-hospitalisation of HCC and

decompensated cirrhosis cases, and (iii) the non-diagnosis of HCV infection among HCC and decompensated cirrhosis cases). There was a 30% increase in the estimated number of new diagnoses for decompensated cirrhosis related to HCV infection from 230 (95% CI 220-250) in 1996-1998 to 300 (280-320) cases in 1999-2001 for all Scotland. In contrast, there was no change in HCC new diagnoses related to HCV infection in Scotland: 52 (95% CI 46-60) cases in 1996-1998 and 49 (42-57) in 1999-2001.

4.4.5 Risk factors for the development of HCC and decompensated cirrhosis among HCV diagnosed persons

The relative hazards in Tables 4.7 and 4.8 show the change in risk of HCC and decompensated cirrhosis, respectively, for each of the epidemiological factors. The highest risk for the development of HCC was associated with cases aged 50 years and above, which remained the only significant factor in the multi-factorial model restricted to referrals for HCV diagnosis from non-hospital settings (relative hazard (RH) 35 with 95% CI 7-169). Cases hospitalised with alcohol abuse (3.4), referrals for HCV diagnosis from hospital (2.8) and males (2.6) were also significantly associated with an increased risk of HCC in the multi-factorial model for all diagnosed cases.

Increasing age was also highly associated with a raised risk of decompensated cirrhosis in the multi-factorial model restricted to referrals from non-hospital settings (RH 4.6 (95% CI 2.2-9.6), 8.8 (3.5-22.0) and 10.7 (3.1-37.5) for those aged 30-49, 50-69 and 70+ years, respectively, compared to those aged <30 years). Significantly increased risk of decompensated cirrhosis was also found with hospitalisation for alcohol abuse and HBV, diagnosis with HIV infection and non-IDU risk for HCV infection (RHs 6.1 (95% CI 4.0-9.1), 2.0 (1.1-3.6), 3.9 (2.2-7.0) and 2.4 (1.4-4.2),

respectively). Broadening to referrals from all settings, cases with unknown risk for HCV infection, referrals for HCV diagnosis from hospital and residents of Lothian also had significantly increased risk of progression to decompensated cirrhosis; males did not have a significantly different risk from females.

Figure 4.1 illustrates the development of decompensated cirrhosis among HCV diagnosed cases according to age and alcohol abuse. Development of decompensated cirrhosis by 50 years of age increased from 14% (95% CI 10-17%) to 46% (37-54%) among cases without and with a history of hospitalisation with alcohol abuse, respectively; restricting to non-hospital referrals for HCV diagnosis, these proportions reduced marginally to 11% (7-15%) and 44% (29-55%), respectively.

4.4.6 Mortality related to HCC and decompensated cirrhosis among HCV diagnosed persons

Tables 4.9(a) and 4.9(b) examine the mortality of HCV diagnosed patients following first hospitalisation for HCC and decompensated cirrhosis during 1991-2001 in Scotland, respectively. The probability of death from HCC and all causes following first hospitalisation with HCC was 57% and 68% at 1 year increasing to 63% and 79% at 2 years, respectively; the risk of death following first hospitalisation with HCC was higher among patients aged 50 years or more and men but neither reached statistical significance. The probability of death from decompensated cirrhosis and all causes following first hospitalisation with decompensated cirrhosis was 18% and 42% at 1 year increasing to 39% and 72% at 5 years, respectively. The risk of all cause death following first hospitalisation with decompensated cirrhosis was significantly higher among those aged 50 years or older at hospitalisation compared to younger patients (RH 1.85; 95% CI 1.46-2.35, $p<0.0001$). The probability of having a liver transplant

within the first two years following first hospitalisation for decompensated cirrhosis was 4.2% (95% CI 1.5-6.9%).

4.4.7 Prevalence of diagnosed HCV infection among all HCC and decompensated cirrhosis cases in Scotland

Seven hundred first hospital admissions and 617 deaths from HCC occurred during 1996-2001 in Scotland (Table 4.10), of which 9.7% (68/700) and 8.1% (50/617) were determined as known to be infected with HCV, respectively. Of the 68 known HCV infected persons hospitalised with HCC, 51 (75%) were determined as HCV infected according to both their SCIEH and either hospital or death records, 6 (9%) from only their SCIEH record and 11 (16%) from either their hospital or death records; 39 (78%), 5 (10%) and 6 (12%) were similarly recognised as known HCV infected among the 50 HCC deaths. Prevalence of known HCV infection was highest among HCC cases aged 30-49 years (39% of 44 new hospitalisations and 40% of 25 deaths). The aetiological factors potentially responsible for HCC were only explained by either (a) alcohol, (b) HBV or (c) HCV recorded in 38% of hospitalised cases (a: 178; b: 13; c: 33; a & b: 5; a & c: 28; b & c: 3; and a, b & c: 4) and 38% of deaths (a: 169; b: 12; c: 28; a & b: 3; a & c: 21; and a, b & c: 1).

New hospital admissions and deaths from decompensated cirrhosis occurred in 10,588 and 3,936 cases, respectively, during 1996-2001 in Scotland (Table 4.10), of which 4.2% (442/10588) and 3.4% (134/3936), respectively, were determined as known to be infected with HCV. Of the 442 known HCV infected persons hospitalised with decompensated cirrhosis, 286 (65%) were determined as HCV infected according to both their SCIEH and either hospital or death records, 64 (14%) from only their SCIEH record and 92 (21%) from either their hospital or death

records; 84 (63%), 23 (17%) and 27 (20%) were similarly recognised as known HCV infected among the 134 decompensated cirrhosis deaths. Prevalence of known HCV infection was highest among decompensated cirrhosis cases aged under 50 years (9% of new hospitalisations and 8% of deaths). Alcohol was identified as a factor in 83% of all decompensated cirrhosis new hospitalisations (other aetiological factors: alcohol (a): 8412; HBV (b): 28; HCV (c): 105; a & b: 53; a & c: 278; b & c: 17; and a, b & c: 42) and 89% of deaths (a: 3378; b: 12; c: 26; a & b: 16; a & c: 88; b & c: 4; and a, b & c: 16).

4.5 Discussion

To help policymakers to prioritise HCV-related interventions and research and to allocate healthcare resources accordingly, accurate information about the current burden of this disease is essential. The greatest burden from HCV infection will come from the long-term complications of this chronic liver disease, namely decompensated cirrhosis and HCC. In the United States, examination of trends in deaths from non-A, non-B viral hepatitis and the frequency of inpatient care for HCV-related diagnoses highlighted that the mortality and healthcare utilisation associated with long-standing HCV infection had increased over the past decade[185,201]. These data, however, relied on the accurate reporting of hepatitis C on death and hospital records and thus, likely, under-estimated the true mortality and morbidity burden. Unless countries introduce national surveillance systems for registration of HCV-related decompensated cirrhosis and HCC, akin to that for AIDS diagnosis, the record-linkage approach developed here is the only means to ascertain these data. The laboratory reporting of diagnostic positive tests for HCV antibodies in Scotland linked electronically to clinical data

gathered from hospital and death records therefore provided a unique national epidemiological dataset on diagnosed HCV infection.

Approximately 500 and 200 diagnosed HCV antibody positive persons in Scotland had developed and died of liver failure, respectively, by the end of 2001. The number of persons with newly developed HCV-related decompensated cirrhosis in Scotland was estimated to increase by 30% from 230 (95% CI 220-250) in 1996-1998 to 300 (280-320) cases in 1999-2001. The number of confirmed HCV antibody positive persons who had presented to hospital with decompensated cirrhosis and HCC by 2001 was, however, a small fraction – only 4.2% (514/12,096) and 0.6% (71/12,096), respectively – of the total HCV diagnosed population in Scotland. This observation may be reassuring for a patient newly diagnosed with HCV, but represents a growing significant burden on healthcare resources.

Estimates of the proportion of chronic liver disease attributable to HCV infection vary considerably, ranging from 8-15% in the United States[201] and New Zealand[202] to 62-74% in Italy[203] and Egypt[204]. Back-calculation models in France assumed that 36%, and more recently 27%, of HCC deaths were attributable to HCV[78,79]. Much higher prevalences of HCV antibodies were reported among selected HCC patients in Japan (60-95%)[205,206] and other parts of Europe (45-75%)[207,208], except in England (22% of 37) and Greece (14% of 56)[209]. Australian projections estimated that 7% (5-8%) of HCC cases in 1998 were due to HCV infection[81]. HCV was detected in 30% of 80 HCC patients, with stored serum samples, presenting to a single hospital in the East of Scotland between 1985 and 1994[39].

In comparison, low prevalences of diagnosed HCV infection were found among individuals with HCC and decompensated cirrhosis (DC) presenting to hospital (10% and 4%, respectively) or having died (8% and 3%, respectively) in

Scotland during 1996-2001. The underlying prevalence of HCV in these groups could be higher at 13% (i.e. hospitalised with HCC), 6% (hospitalised with DC), 11% (died with HCC) and 5% (died with DC), respectively, after accounting for infections which were not identified through record-linkage, because (i) 10% of HCV diagnosed persons could not be included in the record-linkage due to insufficient identifiers, and (ii) a proportion (estimated to be 17.5%, based on the proportion who were HCV diagnosed after hospitalisation with decompensated cirrhosis) of HCV-infected HCC and decompensated cirrhosis cases were not tested and diagnosed with HCV. Estimates were restricted to 1996-2001 to minimise the influence of the sharp increase in HCV antibody testing of patients with liver disease during the early 1990s. Misclassification of the ICD code on the hospital or death record represents a further source of error, although this appears to be minor given that 95% and 91% of HCV diagnosed individuals who had been hospitalised or had died with HCC, respectively, were also registered with HCC on the cancer database. HCC and hepatic decompensation – as manifested by ascites, hepatic encephalopathy or gastrointestinal bleeding – generally necessitate inpatient hospital care. However, 25% and 14% of deaths from HCC and decompensated cirrhosis, respectively, were not identified with these conditions in the hospital register and therefore the hospital morbidity data alone may under-estimate the incidence of severe HCV-disease.

The extent of alcohol- compared to HCV- related hepatic failure is sobering, with hospitalisations associated with the former outnumbering the latter 20-fold, and underlines alcohol as the major cause of chronic liver disease currently in Scotland; although, HCV is forecast to become a more prominent cause in the future (as suggested from projections derived in Chapter 6). Alcohol was also a prominent feature among HCV diagnosed persons who either died or were hospitalised with

decompensated cirrhosis during 1996-2001 (78% and 72%, respectively). The younger age of decompensated patients presenting to hospital with both HCV and alcohol (78% <50 years old) suggests that the combined effect of these two factors accelerates liver disease progression more than with only one (HCV: 48%; alcohol: 33%) or none of these factors (17%). In multiple regression analysis, a history of hospitalisation with an alcohol-related diagnosis was associated with a 5- to 6- fold increased risk of developing decompensated cirrhosis among HCV diagnosed antibody positive individuals in Scotland. A limitation of the hospital data was the absence of information on the quantity of alcohol consumed by patients. Heavy alcohol consumption, particularly above 350g per week, has previously been correlated with increased liver disease progression in individuals infected with HCV[95,210] and is the focus of further study in Chapter 5. In keeping with the literature on the natural history of HCV disease[5], the proportional hazards multifactorial regression also identified older age, HIV and HBV co-infection as factors associated with higher risk of decompensated cirrhosis.

Injecting drug use represents the most common risk factor for HCV infection throughout the industrialised world[211]. However a substantial proportion of persons who test positive for HCV antibodies report no risk factors for infection. Thirty percent of persons with acute HCV in the United States during 1991-1995 denied a specific exposure associated with acquiring infection during the six months preceding onset of their illness, although over half of these reported a previous history of drug use[212]. In England and Wales, 43% of confirmed HCV infections during 1992-1996 lacked risk factor information[213]. It follows that either the potential risk factors for HCV acquisition were not carefully elicited or that there may be a significant undefined source of viral transmission. A study in the United States showed that the

route of HCV acquisition could be delineated in 88% of HCV chronically infected patients using a systematic interview approach; in nearly all cases, the initially unreported risk factor for HCV transmission was a remote history of injecting drug use[214]. This application in Scotland of capture-recapture methodology is the first to demonstrate the use of log-linear modelling, based on record-linkage data from four sources (i.e. HCV diagnoses, HIV test, hospital and death records), to estimate the proportion of IDUs among HCV diagnosed persons. Of 12,096 HCV antibody positive persons studied, 61% reported injecting drug use with their HCV diagnosis and a further 27%, yielding a total of 88%, were established as IDUs through log-linear modelling.

This study provided the first estimates of the current morbidity and mortality associated with diagnosed HCV infection in Scotland, which is of particular importance in terms of validating HCV projections in Chapter 6, and highlighted the impact of alcohol on the course of this epidemic. The extent of heavy drinking among IDUs – reported from other countries to be in the range of 20% to 50%[215,216,217,218] – has received insufficient attention in the treatment and care of this client group. Further research is required to assess the influence on drinking behaviour of testing IDUs, including those who have ceased injecting, for HCV antibodies and counselling them about the consequences of alcohol[219]. In light of the apparent synergistic effect between alcohol and HCV, limiting the alcohol consumption of chronically infected individuals is essential to help prevent future morbidity and mortality related to HCV infection.

Table 4.1: Characteristics of HCV diagnosed individuals in Scotland up to the end of 2001: comparison between 12,096 and 1,275 cases who had sufficient (linked) and insufficient (non-linked) identifiers, respectively, as required to allow record-linkage with other data sources.

		HCV diagnosed persons N (%)		**Odds Ratio for non-linked (95% CI)**	
		Linked N=12,096	Non-linked N=1,275	Uni-factorial	Multi-factorial
Year of HCV diagnosis	Pre 1994	1187 (10%)	52 (4%)	**0.35 (0.27-0.47)**	**0.24 (0.14-0.40)**
	1994-1997	4257 (35%)	396 (31%)	**0.75 (0.66-0.85)**	0.87 (0.73-1.05)
	1998-2001	6652 (55%)	827 (65%)	1.00 (Baseline)	1.00 (Baseline)
Gender	Male	8345 (69%)	831 (71%)	1.00 (Baseline)	1.00 (Baseline)
(129 not known)	Female	3723 (31%)	343 (29%)	0.93 (0.81-1.05)	0.90 (0.75-1.09)
Age at HCV diagnosis (years)	< 20	563 (5%)	59 (6%)	1.05 (0.80-1.39)	0.93 (0.63-1.37)
(277 not known)	20-34	7507 (62%)	747 (75%)	1.00 (Baseline)	1.00 (Baseline)
	35-49	3154 (26%)	179 (18%)	**0.57 (0.48-0.67)**	**0.51 (0.41-0.64)**
	≥ 50	872 (7%)	13 (1%)	**0.15 (0.09-0.26)**	**0.23 (0.13-0.42)**
Risk group	IDU	7327 (61%)	716 (56%)	1.00 (Baseline)	1.00 (Baseline)
	Non-IDU	895 (7%)	45 (4%)	**0.52 (0.38-0.70)**	1.19 (0.76-1.86)
	None reported	3874 (32%)	514 (40%)	**1.36 (1.20-1.53)**	**2.82 (2.32-3.42)**
Healthboard of residence for HCV diagnosis	Greater Glasgow	4513 (37%)	445 (35%)	1.00 (Baseline)	1.00 (Baseline)
	Lothian	1859 (15%)	112 (9%)	**0.61 (0.50-0.76)**	**0.51 (0.38-0.69)**
	Grampian	1360 (11%)	209 (16%)	**1.56 (1.31-1.86)**	**1.97 (1.48-2.62)**
	Tayside	986 (8%)	72 (6%)	**0.74 (0.57-0.96)**	0.84 (0.57-1.22)
	Rest of Scotland	3378 (28%)	437 (34%)	**1.31 (1.14-1.51)**	**2.30 (1.86-2.85)**
Referral source for HCV diagnosis	Hospital	5755 (49%)	311 (25%)	1.00 (Baseline)	1.00 (Baseline)
(384 not known)	GP	2633 (22%)	67 (5%)	**0.47 (0.36- 0.61)**	**0.57 (0.38- 0.85)**
	Drug/Counselling Clinic	1047 (9%)	195 (16%)	**3.45 (2.85- 4.17)**	**11.68 (9.09- 15.01)**
	Prison	1054 (9%)	55 (4%)	0.97 (0.72- 1.30)	**1.60 (1.12- 2.30)**
	GUM clinic	316 (3%)	529 (42%)	**30.98 (25.87-37.09)**	**124.94 (96.47-161.80)**
	Other	933 (8%)	92 (7%)	**1.82 (1.43- 2.33)**	1.03 (0.61- 1.74)

Table 4.2: Epidemiological characteristics of HCV diagnosed individuals in Scotland, who were linked to hospital admission, deaths and HIV testee databases, by risk group.

			Risk Group reported with HCV diagnosis		
			IDU N=7327	Non-IDU N=895	None reported N=3874
(a) Characteristics extracted from the HCV diagnosis record					
Year of HCV diagnosis	Pre 1994		534 (7%)	327 (37%)	326 (8%)
	1994-1997		2467 (34%)	315 (35%)	1475 (38%)
	1998-2001		4326 (59%)	253 (28%)	2073 (54%)
Gender	Male		5245 (72%)	583 (65%)	2517 (65%)
(28 not known)	Female		2075 (28%)	311 (35%)	1337 (35%)
Age at HCV diagnosis (years)	< 20		346 (5%)	107 (12%)	110 (3%)
	20-34		5344 (73%)	344 (38%)	1819 (47%)
	35-49		1577 (22%)	290 (32%)	1287 (33%)
	≥ 50		60 (1%)	154 (17%)	658 (17%)
Healthboard of residence	Greater Glasgow		2845 (39%)	253 (28%)	1415 (37%)
For HCV diagnosis	Lothian		1182 (16%)	208 (23%)	469 (12%)
	Grampian		978 (13%)	74 (8%)	308 (8%)
	Tayside		618 (8%)	99 (11%)	269 (7%)
	Rest of Scotland		1704 (23%)	261 (29%)	1413 (36%)
Referral source for HCV diagnosis	Hospital		2936 (41%)	322 (37%)	2497 (67%)
(358 not known)	GP		1901 (27%)	177 (20%)	555 (15%)
	Drug/Counselling Clinic		865 (12%)	33 (4%)	149 (4%)
	Prison		890 (12%)	8 (1%)	156 (4%)
	GUM clinic		263 (4%)	28 (3%)	25 (1%)
	Other		308 (4%)	305 (35%)	320 (9%)
(b) Characteristics extracted from matched records on the hospital admission and deaths databases					
Matched to hospital & deaths	No		1274 (17%)	148 (17%)	799 (21%)
databases	Only deaths		31 (<1%)	1 (<1%)	11 (<1%)
	Only hospital		5259 (72%)	630 (70%)	2520 (65%)
	Both hospital and deaths		763 (10%)	116 (13%)	544 (14%)
Deprivation status*	High		3655 (61%)	281 (38%)	1533 (50%)
on matched records (62 missing)	Low-Medium		2360 (39%)	455 (62%)	1529 (50%)
Alcohol mentioned	Yes		1251 (21%)	99 (13%)	657 (21%)
on matched records	No		4802 (79%)	648 (87%)	2418 (79%)
Hepatitis B virus mentioned	Yes		558 (9%)	36 (5%)	188 (6%)
on matched records	No		5495 (91%)	711 (95%)	2887 (94%)
(c) Characteristics extracted from matched records on the HIV testee database					
Diagnosed HIV positive	Yes		354 (5%)	42 (5%)	15 (<1%)
	No		6973 (95%)	853 (95%)	3859 (100%)

* The highest deprivation score recorded on any matched hospital admission or death record, where deprivation was assigned according to carstairs seven-point scale with high categorised as score 6-7 and low-medium as score 1-5.

Table 4.3: IDU status of 12,096 HCV diagnosed individuals in Scotland according to 4 data-sources (HCV diagnoses, HIV test, hospital discharge and death databases) and the estimated number of HCV diagnosed IDUs from log-linear modelling.

IDU identified from 4 data sources (Y=yes; N=no)				**Observed number of HCV diagnosed persons**		**Estimated number of HCV diagnosed IDUs from log-linear model***
(A) HCV Diagnoses	**(B) HIV test**	**(C) Hospital Discharge**	**(D) Death**			
Y	Y	Y	Y	50		53
N	Y	Y	Y	11		8
Y	N	Y	Y	23		24
N	N	Y	Y	8		7
Y	Y	N	Y	117		113
N	Y	N	Y	18		22
Y	N	N	Y	40		40
N	N	N	Y	34		34
Y	Y	Y	N	1027		1024
N	Y	Y	N	142		145
Y	N	Y	N	859		858
N	N	Y	N	248		249
Y	Y	N	N	2383		2387
N	Y	N	N	456		452
Y	N	N	N	2828		2828
N	N	N	N	-		2404
Total number of HCV diagnosed IDUs identified from data-sources				**8244**		**8244**
Total number of HCV diagnosed IDUs, including those not identified from data-sources (95% confidence interval)						**10648 (9753 - 12047)**

* Log-linear model (residual deviance of 2.6 on 3 df) included main effects for data-sources (A) HCV diagnoses, (B) HIV test, (C) hospital discharge and (D) deaths (model coefficients (standard errors): A –0.63 (0.03); B 0.05 (0.04); C 0.58 (0.04); D 1.73 (0.04)), with interactions between data-sources A and B (0.28 (0.03)); A and C (0.17 (0.03)); B and C (0.11 (0.04)); B and D (0.23 (0.04)); C and D (0.10 (0.04)); A, B and C (0.10 (0.03)); and B, C and D (0.07 (0.03)).

Table 4.4: Characteristics of first hospital admissions and deaths from HCC and decompensated cirrhosis among diagnosed HCV positive individuals in Scotland during 1991-2001.

		HCC			Decompensated cirrhosis		
		First hospital admission	Deaths		First hospital admission	Deaths	
			Underlying cause	Underlying or contributing cause		Underlying cause	Underlying or contributing cause
All Scotland		71 (100%)	59 (100%)	67 (100%)	514 (100%)	75 (100%)	196 (100%)
• **Risk group**	IDU	8 (11%)	6 (10%)	7 (10%)	157 (30%)	21 (28%)	62 (31%)
	IDU (based on record-linkage)*	0 (0%)	0 (0%)	0 (0%)	29 (6%)	8 (11%)	13 (7%)
	Non-IDU	11 (16%)	6 (10%)	8 (12%)	60 (12%)	3 (4%)	21 (11%)
	Not known	52 (73%)	47 (80%)	52 (78%)	268 (52%)	43 (57%)	100 (51%)
• **Age at hospital admission or death (years)**	< 30	0 (0%)	1 (2%)	1 (2%)	33 (6%)	1 (1%)	10 (5%)
	30-49	13 (18%)	9 (15%)	10 (15%)	325 (63%)	57 (76%)	116 (59%)
	50-69	36 (51%)	24 (41%)	26 (39%)	112 (22%)	15 (20%)	49 (25%)
	≥ 70	22 (31%)	25 (42%)	30 (45%)	44 (9%)	2 (3%)	21 (11%)
• **Gender**	Male	60 (85%)	46 (78%)	53 (79%)	386 (75%)	59 (79%)	143 (73%)
	Female	11 (15%)	13 (22%)	14 (21%)	128 (25%)	16 (21%)	53 (27%)
• **Deprivation status****	High	25 (35%)	21 (36%)	23 (35%)	264 (52%)	48 (64%)	109 (56%)
	Low-Medium	46 (65%)	37 (64%)	43 (65%)	246 (48%)	27 (36%)	87 (44%)
	(not known)	(0)	(1)	(1)	(4)	(0)	(0)
• **Admission/death in time since HCV diagnosis**	>14 days before	4 (6%)	2 (3%)	2 (3%)	90 (17%)	0 (0%)	0 (0%)
	within 14 days	20 (28%)	2 (3%)	3 (4%)	133 (26%)	4 (5%)	23 (12%)
	>14 days after HCV diagnosis	47 (66%)	55 (93%)	62 (93%)	291 (57%)	71 (95%)	173 (88%)
• **Alcohol mentioned†**	Yes	29 (41%)	23 (39%)	27 (40%)	364 (71%)	73 (97%)	138 (70%)
	No	42 (59%)	36 (61%)	40 (60%)	150 (29%)	2 (3%)	58 (30%)
• **Diagnosed HIV positive**	Yes	0 (0%)	0 (0%)	0 (0%)	28 (5%)	2 (3%)	16 (8%)
	No	71 (100%)	59 (100%)	67 (100%)	486 (94%)	73 (97%)	180 (92%)
• **HBV mentioned†**	Yes	6 (9%)	2 (3%)	3 (5%)	64 (13%)	8 (11%)	28 (14%)
	No	65 (91%)	57 (97%)	64 (95%)	450 (87%)	67 (89%)	168 (86%)
• **Healthboard of residence for HCV diagnosis**	Greater Glasgow	18 (25%)	21 (36%)	22 (33%)	173 (34%)	33 (44%)	65 (33%)
	Lothian	24 (34%)	20 (34%)	23 (34%)	142 (28%)	18 (24%)	63 (32%)
	Grampian	5 (7%)	1 (2%)	1 (1%)	36 (7%)	2 (3%)	7 (4%)
	Tayside	5 (7%)	3 (5%)	3 (5%)	40 (8%)	3 (4%)	12 (6%)
	Rest of Scotland	19 (27%)	14 (24%)	18 (27%)	123 (24%)	19 (25%)	49 (25%)

* Individuals who had no information on risk from their HCV diagnosis were assigned as IDUs according to data recorded on their HIV test, hospital admission or death records; ** Carstairs seven-point deprivation scale: high represented score 6-7, low-medium represented score 1-5; † Mentioned on any of individual's hospital admission records or death record.

Table 4.5: Year of HCV diagnosis for cases hospitalised for the first time with decompensated cirrhosis during 1996-2000.

Hospitalisations for decomp. cirrhosis		**HCV diagnosed prior to or in year of hospitalisation**	**Year of HCV diagnosis for cases diagnosed after hospital admission**					
Year	**N**	**N_1**	**1997**	**1998**	**1999**	**2000**	**2001**	**Total**
1996	42	39	0	3	0	0	0	3
1997	58	53	-	1	0	3	1	5
1998	71	68	-	-	2	1	0	3
1999	78	74	-	-	-	2	2	4
2000	66	59	-	-	-	-	7	7

Table 4.6: Estimated new diagnoses (and 95% confidence interval) for HCC and decompensated cirrhosis related to HCV infection in Greater Glasgow and Scotland during 1996-2001*.

Region	Condition	Calendar year						Total
		1996	1997	1998	1999	2000	2001	
Scotland	HCC	18 (16-21)	27 (24-31)	7 (6- 8)	16 (14-19)	13 (11-15)	20 (17-23)	101 (88-117)
Greater Glasgow	HCC	4 (3- 4)	5 (5- 6)	2 (2- 2)	4 (3- 4)	4 (3- 4)	4 (3- 4)	23 (19- 24)
Scotland	Decomp. cirrhosis	55 (51-59)	78 (73-84)	98 (92-106)	109 (102-118)	86 (80-92)	100 (94-108)	526 (492-567)
Greater Glasgow	Decomp. cirrhosis	20 (19-22)	26 (25-28)	31 (29- 33)	40 (38- 43)	34 (32-37)	28 (26- 30)	179 (169-193)

* The annual number of first hospital admissions for HCC and decompensated cirrhosis among individuals who were already HCV diagnosed prior to hospitalisation or within 14 days were adjusted to account for (i) the inability to link a proportion of HCV diagnosed cases due to insufficient identifiers (by a factor of 13371/12096 for all Scotland and 4958/4513 for Greater Glasgow, Table 4.1), (ii) the non-hospitalisation of HCC and decompensated cirrhosis cases (sampled from the distributions of the proportion of deaths not previously hospitalised for these conditions (see Results 4.4.3): 25.4% (95% CI 15.9-37.7%) for HCC and 14.3% (95% CI 9.9-20.2%) for decompensated cirrhosis), and (iii) the non-diagnosis of HCV infection among HCC and decompensated cirrhosis cases (sampled from the distribution of the proportion of hospitalised decompensated cirrhosis cases who were not diagnosed with HCV infection until >14 days after their hospitalisation (see Results 4.4.3): 17.5% (95% CI 14.4-21.1)).

Table 4.7: Cox proportional hazards regression used to assess the influence of epidemiological risk factors on the development of HCC following HCV diagnosis in Scotland.

		All HCV diagnosed cases				HCV diagnosed cases referred from non-hospital settings			
		Person years at risk (py)	Number of HCC (rate per 1000 py)	Relative Hazard (95% CI) Uni-factorial	Relative Hazard (95% CI) Multi-factorial	Person years at risk (py)	Number of HCC (rate per 1000 py)	Relative Hazard (95% CI) Uni-factorial	Relative Hazard (95% CI) Multi-factorial
Baseline characteristics at HCV diagnosis									
Gender	Male	29680	51 (1.7)	**2.12 (1.11- 4.07)**	**2.61 (1.35- 5.05)**	15686	11 (0.7)	3.97 (0.51-30.70)	4.62 (0.60-35.83)
	Female	13586	11 (0.8)	1.00 (Baseline)	1.00 (Baseline)	5477	1 (0.2)	1.00 (Baseline)	1.00 (Baseline)
Risk Group	IDU	24830	7 (0.3)	1.00 (Baseline)	1.00 (Baseline)	14093	3 (0.2)	1.00 (Baseline)	1.00 (Baseline)
	Non-IDU	4714	13 (2.8)	**10.20 (4.04-25.70)**	2.56 (0.96- 6.85)	3094	7 (2.3)	**10.54 (2.67-41.60)**	2.13 (0.37-12.14)
	Not known	13835	42 (3.0)	**10.90 (4.88-24.10)**	2.26 (0.95- 5.42)	4017	2 (0.5)	2.35 (0.39-14.00)	1.13 (0.18- 7.30)
Health-board of residence	Greater Glasgow	15564	16 (1.0)	1.00 (Baseline)	1.00 (Baseline)	6700	4 (0.6)	1.00 (Baseline)	1.00 (Baseline)
	Lothian	8440	19 (2.3)	**2.20 (1.13- 4.30)**	1.53 (0.78- 3.00)	6306	3 (0.5)		
	Grampian	4433	4 (0.9)	0.87 (0.29- 2.61)	0.83 (0.28- 2.49)	2239	1 (0.4)	0.83 (0.25- 2.78)	0.62 (0.18- 2.07)
	Tayside	3794	7 (1.8)	1.79 (0.74- 4.36)	1.53 (0.61- 3.83)	1763	3 (1.7)		
	Rest of Scotland	11147	16 (1.4)	1.39 (0.70- 2.78)	0.71 (0.35- 1.43)	4195	1 (0.2)		
Referral source for HCV diagnosis	Hospital	20746	48 (2.3)	**4.10 (2.18- 7.72)**	**2.80 (1.42- 5.52)**	-	-	-	-
	Non-hospital setting	21203	12 (0.6)	1.00 (Baseline)	1.00 (Baseline)	-	-	-	-
	Not known	1429	2 (1.4)	2.53 (0.57-11.33)	1.59 (0.33- 7.73)	-	-	-	-
Time-dependent characteristics									
Current age	< 50	39708	9 (0.2)	1.00 (Baseline)	1.00 (Baseline)	19844	3 (0.2)	1.00 (Baseline)	1.00 (Baseline)
	50+	3670	53 (14.4)	**75.00 (35.90-157.0)**	**38.17 (18.10-80.49)**	1359	9 (6.6)	**22.80 (7.04-74.10)**	**34.47 (7.04-168.8)**
Hospitalisation for alcohol abuse	Yes	5025	16 (3.2)	**2.66 (1.50- 4.69)**	**3.38 (1.87- 6.09)**	2162	1 (0.5)	0.79 (0.10- 6.11)	0.99 (0.12- 8.17)
	No	38353	46 (1.2)	1.00 (Baseline)	1.00 (Baseline)	19041	11 (0.6)	1.00 (Baseline)	1.00 (Baseline)
Diagnosed HIV positive	Yes	1725	0 (0.0)	-	-	1039	0 (0.0)	-	-
	No	41653	62 (1.5)	-	-	20164	12 (0.6)	-	-
Hospitalisation for HBV	Yes	2446	3 (1.2)	0.87 (0.27- 2.75)	0.91 (0.28- 2.97)	1042	1 (1.0)	1.60 (0.21-12.40)	1.31 (0.16-11.05)
	No	40932	59 (1.4)	1.00 (Baseline)	1.00 (Baseline)	20161	11 (0.5)	1.00 (Baseline)	1.00 (Baseline)

Table 4.8: Cox proportional hazards regression used to assess the influence of epidemiological risk factors on the development of decompensated cirrhosis (DC) following diagnosis of HCV positive individuals in Scotland.

			All HCV diagnosed cases				HCV diagnosed cases referred from non-hospital settings			
			Person years at risk (py)	Number of DC (rate per 1000 py)	Relative Hazard (95% CI)		Person years at risk (py)	Number of DC (rate per 1000 py)	Relative Hazard (95% CI)	
					Uni-factorial	Multi-factorial			Uni-factorial	Multi-factorial
Baseline characteristics at HCV diagnosis										
Gender	Male		29005	228 (7.9)	**1.28 (1.00- 1.65)**	1.27 (0.98- 1.64)	15521	81 (5.2)	1.16 (0.73- 1.83)	1.07 (0.67- 1.70)
	Female		13369	82 (6.1)	1.00 (Baseline)	1.00 (Baseline)	5443	24 (4.4)	1.00 (Baseline)	1.00 (Baseline)
Risk Group	IDU		24584	122 (5.0)	1.00 (Baseline)	1.00 (Baseline)	13998	58 (4.1)	1.00 (Baseline)	1.00 (Baseline)
	Non-IDU		4584	46 (10.0)	**2.13 (1.51- 3.00)**	**1.93 (1.33- 2.79)**	3065	26 (8.5)	**1.87 (1.15- 3.03)**	**2.42 (1.40- 4.18)**
	Not known		13318	142 (10.7)	**2.17 (1.70- 2.77)**	**1.63 (1.22- 2.16)**	3940	21 (5.3)	1.26 (0.76- 2.07)	1.56 (0.90- 2.67)
Health-board of residence	Greater Glasgow		15242	104 (6.8)	1.00 (Baseline)	1.00 (Baseline)	6642	28 (4.2)	1.00 (Baseline)	1.00 (Baseline)
	Lothian		8180	94 (11.5)	**1.74 (1.31- 2.30)**	**1.51 (1.12- 2.05)**	6217	49 (7.9)	**1.81 (1.13- 2.91)**	1.18 (0.71- 1.95)
	Grampian		4393	20 (4.6)	0.66 (0.41- 1.07)	0.69 (0.42- 1.11)	2227	8 (3.6)	0.89 (0.41- 1.95)	0.92 (0.42- 2.05)
	Tayside		3728	24 (6.4)	0.96 (0.62- 1.49)	0.85 (0.54- 1.35)	1755	6 (3.4)	0.83 (0.34- 2.00)	0.78 (0.32- 1.90)
	Rest of Scotland		10942	68 (6.2)	0.90 (0.66- 1.22)	0.73 (0.54- 1.00)	4163	14 (3.4)	0.78 (0.41- 1.48)	0.72 (0.37- 1.37)
Referral source	Hospital		20078	192 (9.6)	**1.92 (1.51- 2.44)**	**1.81 (1.39- 2.35)**	-	-	-	-
	Non-hospital setting		21004	105 (5.0)	1.00 (Baseline)	1.00 (Baseline)	-	-	-	-
	Not known		1404	13 (9.3)	**1.92 (1.08- 3.42)**	**1.88 (1.01- 3.50)**	-	-	-	-
Time-dependent characteristics										
Current age	< 30		13692	20 (1.5)	1.00 (Baseline)	1.00 (Baseline)	7331	8 (1.1)	1.00 (Baseline)	1.00 (Baseline)
	30-49		25364	197 (7.8)	**6.08 (3.83- 9.65)**	**4.56 (2.86- 7.27)**	12348	79 (6.4)	**6.04 (2.90-12.60)**	**4.59 (2.19- 9.64)**
	50-69		2656	68 (25.6)	**20.27 (12.27-33.48)**	**15.02 (8.91-25.30)**	1070	14 (13.1)	**11.82 (4.89-28.60)**	**8.79 (3.52-21.97)**
	70+		773	25 (32.3)	**24.94 (13.83-44.98)**	**18.45 (9.96-34.15)**	254	4 (15.7)	**14.77 (4.42-49.30)**	**10.69 (3.05-37.47)**
Hospitalisation for alcohol abuse	Yes		4613	107 (23.2)	**4.36 (3.45- 5.51)**	**4.63 (3.64- 5.89)**	2062	40 (19.4)	**5.81 (3.92- 8.63)**	**6.06 (4.04- 9.08)**
	No		37873	203 (5.4)	1.00 (Baseline)	1.00 (Baseline)	18941	65 (3.4)	1.00 (Baseline)	1.00 (Baseline)
Diagnosed HIV positive	Yes		1683	30 (17.8)	**2.69 (1.85- 3.93)**	**2.74 (1.81- 4.16)**	1018	20 (19.7)	**4.61 (2.81- 7.55)**	**3.94 (2.23- 6.96)**
	No		40803	280 (6.9)	1.00 (Baseline)	1.00 (Baseline)	19986	85 (4.3)	1.00 (Baseline)	1.00 (Baseline)
Hospitalisation for HBV	Yes		2334	30 (12.9)	**1.93 (1.32- 2.82)**	**1.70 (1.16- 2.50)**	1006	12 (11.9)	**2.61 (1.43- 4.77)**	**1.95 (1.06- 3.60)**
	No		40152	280 (7.0)	1.00 (Baseline)	1.00 (Baseline)	19997	93 (4.7)	1.00 (Baseline)	1.00 (Baseline)

Figure 4.1: Development of decompensated cirrhosis for HCV diagnosed individuals in Scotland following their diagnosis of HCV according to age and alcohol abuse.

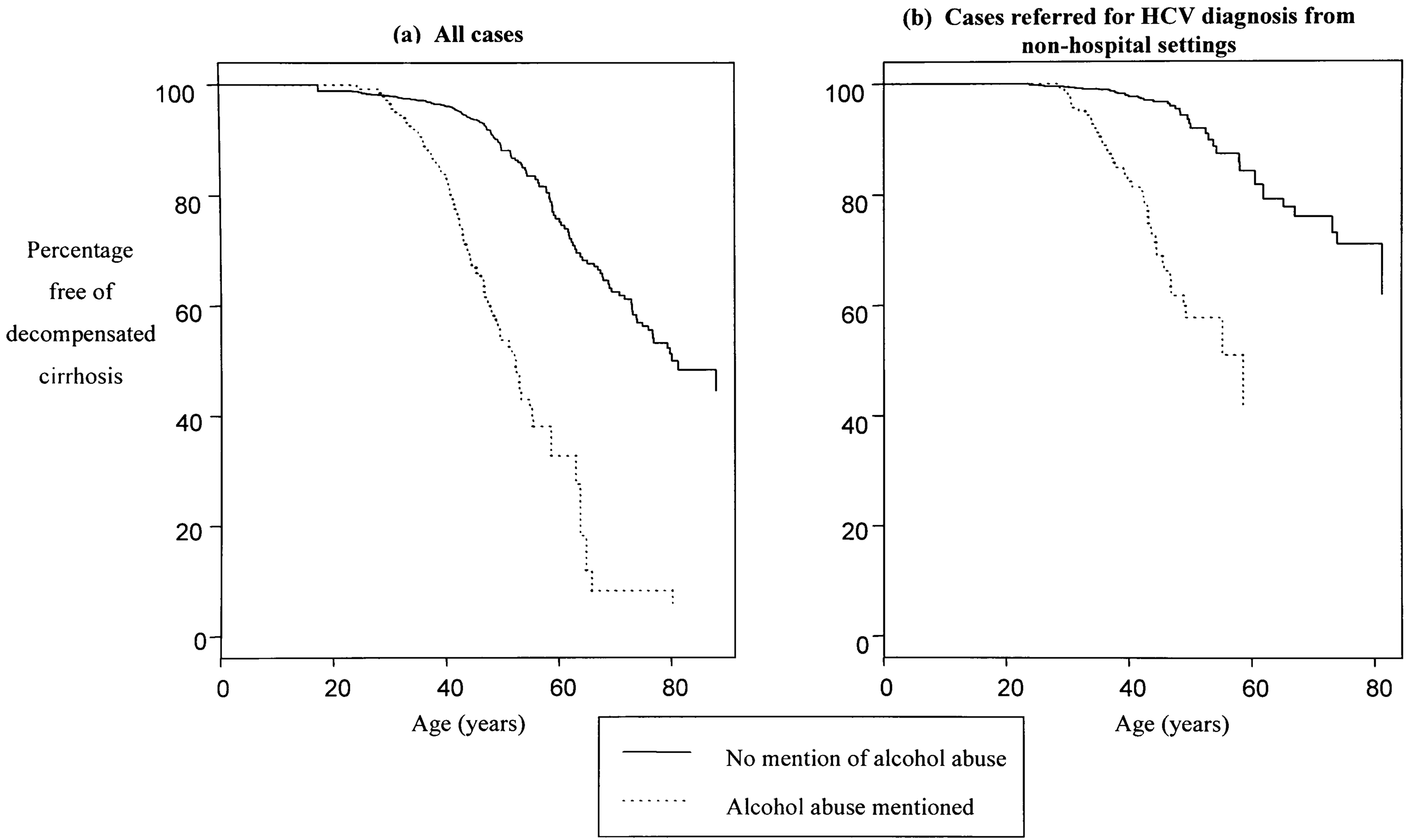


Table 4.9(a): Mortality following first hospitalisation with HCC during 1991-2001 for HCV diagnosed persons in Scotland.

		Number with HCC	Person years at risk	Liver transplant (in cases without DC)	HCC deaths	All deaths	Probability of death from HCC (%, 95% CI)†			Probability of death from all causes (%, 95% CI)†		
							At 1 year	At 2 years	p-value	At 1 year	At 2 years	p-value
Total		70	48.3	8 (1)	43	54	57.1 (42.2-68.1)	63.1 (46.9-74.3)	-	68.3 (54.0-78.2)	78.8 (64.4-87.4)	-
Age at hospitalisation (years)	< 50	13	9.4	4 (0)	7	9	52.2 (7.6-75.2)	52.2 (7.6-75.2)	0.43	59.8 (15.2-80.9)	59.8 (15.2-80.9)	0.33
	50 +	57	38.9	4 (1)	36	45	57.7 (41.4-69.4)	65.1 (46.7-77.2)		69.6 (53.8-80.0)	81.9 (65.9-90.4)	
Gender	Male	59	35.6	7 (1)	35	45	58.5 (41.4-70.6)	66.7 (47.2-78.9)	0.82	70.0 (53.8-80.5)	83.0 (66.7-91.3)	0.43
	Female	11	12.6	1 (0)	8	9	49.7 (10.9-71.6)	63.1 (14.3-84.1)		58.1 (17.5-78.8)	69.3 (23.2-87.7)	

DC Decompensated cirrhosis. † Derived from cox proportional hazards model.

Table 4.9(b): Mortality following first hospitalisation with decompensated cirrhosis (DC) during 1991-2001 for HCV diagnosed persons in Scotland.

		Number with DC	Person years at risk	Liver transplant	DC deaths	All deaths	Probability of death from DC (%, 95% CI) †				Probability of death from all causes (%, 95% CI) †			
							At 1 year	At 2 years	At 5 years	p-value	At 1 year	At 2 years	At 5 years	p-value
Total		507	943.6	16	114	303	17.8 (14.0-21.5)	22.9 (18.3-27.2)	39.4 (31.6-46.3)	-	42.1 (37.5-46.4)	52.3 (47.4-56.8)	71.6 (65.8-76.4)	-
Age at hospitalisation (years)	< 50	352	736.5	9	78	188	16.4 (12.0-20.6)	22.3 (17.0-27.3)	35.2 (26.8-42.7)	0.12	35.7 (30.4-40.7)	47.3 (41.4-52.6)	63.6 (56.5-69.6)	<0.0001
	50 +	155	207.1	7	36	115	21.1 (13.1-28.4)	22.9 (14.2-30.8)	50.4 (31.3-64.2)		57.4 (48.6-64.7)	63.9 (55.0-71.1)	87.2 (77.5-92.7)	
Gender	Male	379	741.5	11	83	220	16.1 (11.8-20.1)	20.9 (15.7-25.7)	39 8 (30.6-47.9)	0.32	40.3 (34.9-45.2)	50.6 (44.8-55.8)	71.7 (64.8-77.2)	0.23
	Female	128	202.1	5	31	83	22.8 (14.1-30.7)	28.5 (18.4-37.3)	*		47.0 (37.4-55.0)	56.7 (46.8-64.7)	69.6 (57.4-78.3)	

* Insufficient data to estimate. † Derived from cox proportional hazards model.

Table 4.10: Characteristics (including HCV diagnosed status*) of all first hospital admissions and deaths from HCC and decompensated cirrhosis in Scotland during 1996-2001.

		HCC				Decompensated cirrhosis			
		First hospital admissions		Deaths		First hospital admissions		Deaths	
		N (%)	HCV diagnosed (% of N)	N (%)	HCV diagnosed (% of N)	N (%)	HCV diagnosed (% of N)	N (%)	HCV diagnosed (% of N)
Total (1996-2001)		700 (100%)	68 (9.7%)	617 (100%)	50 (8.1%)	10588 (100%)	442 (4.2%)	3936 (100%)	134 (3.4%)
Year	1996-1997	240 (34%)	31 (12.9%)	209 (34%)	22 (10.5%)	3149 (30%)	114 (3.6%)	1078 (27%)	28 (2.6%)
	1998-1999	210 (30%)	13 (6.2%)	213 (34%)	10 (4.7%)	3548 (33%)	167 (4.7%)	1242 (32%)	55 (4.4%)
	2000-2001	250 (36%)	24 (9.6%)	195 (32%)	18 (9.2%)	3891 (37%)	161 (4.1%)	1616 (41%)	51 (3.2%)
Gender	Male	496 (71%)	58 (11.7%)	453 (73%)	41 (9.1%)	6809 (64%)	329 (4.8%)	2556 (65%)	96 (3.8%)
	Female	204 (29%)	10 (4.9%)	164 (27%)	9 (5.5%)	3779 (36%)	113 (3.0%)	1380 (35%)	38 (2.8%)
Age (years)	< 30	8 (1%)	0 (0.0%)	5 (1%)	0 (0.0%)	225 (2%)	19 (8.4%)	39 (1%)	4 (10.3%)
	30-49	44 (6%)	17 (38.6%)	25 (4%)	10 (40.0%)	3205 (30%)	290 (9.0%)	1077 (27%)	86 (8.0%)
	50-69	337 (48%)	34 (10.1%)	268 (43%)	20 (7.5%)	5521 (52%)	97 (1.8%)	2175 (55%)	31 (1.4%)
	≥ 70	311 (44%)	17 (5.5%)	319 (52%)	20 (6.3%)	1637 (16%)	36 (2.2%)	645 (16%)	13 (2.0%)
Alcohol mentioned†	Yes	215 (31%)	32 (14.9%)	194 (31%)	22 (11.3%)	8785 (83%)	320 (3.6%)	3498 (89%)	104 (3.0%)
	No	485 (69%)	36 (7.4%)	423 (69%)	28 (6.6%)	1803 (17%)	122 (6.8%)	438 (11%)	30 (6.8%)

* HCV diagnosed based on SCIEH's HCV diagnoses database and mention of HCV on hospital admission or death records.

† Mentioned on any of individual's hospital admission records or death record.

Chapter 5: Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis

5.1 Introduction

Cohort studies of hepatitis C virus (HCV) infection in community-based settings have reported a generally slow course of liver disease[94], although several viral, host and environmental factors appear to accelerate this progression[5,220]. Elucidation of the factors that influence progression to severe HCV disease is essential, both at an individual level, to counsel those affected and help make decisions regarding antiviral therapy, and at a population level, to accommodate covariate influences in projection models aimed at estimating the future burden of disease. An understanding of the parameters affecting the natural history of HCV would also inform models of the cost-effectiveness of preventive and therapeutic interventions[220].

Characteristics commonly associated with an increased risk of progression to cirrhosis include male sex, older age at HCV acquisition and co-infection with HIV[5,220]. A recent meta-analysis estimated the overall relative risk of decompensated liver disease or histological cirrhosis to be 2.9 (95% CI 1.7-5.0) in HIV and HCV co-infected patients compared to those with only HCV infection[221]. Similar relative risks for cirrhosis have been reported in studies of HCV chronically infected persons with heavy alcohol consumption, defined at different thresholds: 2.9 (95% CI 1.6-5.4)[222] and 2.8 (1.1-7.4)[223] with at least 560g and 20 units (equivalent of approximately 240g) of alcohol per week, respectively. Some studies however have failed to identify a significant correlation between heavy alcohol consumption (defined in the range of at least 240 to 560g per week) and development of severe HCV disease[210,224,225,226,227]. Meanwhile, a case-control study (involving 285 cases with liver decompensation and

417 controls with acute diseases unrelated to alcohol) has demonstrated the combined multiplicative effect of alcohol and HCV infection, with a 9 (95% CI 2-43), 15 (7-32) and 147 (42-514) times higher odds of developing cirrhosis in HCV–infected patients who had never consumed alcohol and in HCV–uninfected and HCV–infected patients with lifetime daily alcohol intake of at least 175g, respectively, compared to HCV–uninfected patients who had never consumed alcohol[180].

The long-term follow-up of acute non-A, non-B hepatitis cases in the United States provided an early indication of the importance of alcohol in progression to cirrhosis, with almost four-fifths of liver disease deaths (14/18) associated with alcoholism[228]. The record-linkage of 12,096 HCV diagnosed positive persons in Scotland to hospital admission data, presented in Chapter 4, identified alcohol as a factor in 71% of 514 cases developing HCV-related liver failure during 1991-2001. Populations in which heavy alcohol consumption is relatively common – such as injecting drug users (IDUs)[215,216,217,218], the group most affected by HCV infection in resource-rich countries – will therefore likely experience a higher burden of advanced liver disease among those with chronic HCV than estimated from community-based studies (with 10% heavy alcohol intake)[93].

A convincing, yet inconsistent, pattern has emerged which demonstrates increased progression of HCV-related liver disease with heavy alcohol use. The aim in this chapter was to perform a meta-analysis of published studies that explored the relationship between advanced liver disease and the consumption of alcohol among HCV chronically infected persons. Estimation of the relative risk of cirrhosis associated with heavy alcohol use will inform the design of the HCV projection model described in Chapter 6. Further, the effect of potential sources of heterogeneity –

particularly, the threshold used to define heavy alcohol use – on the pooled relative risk estimate was examined to help explain the inconsistency between study findings.

5.2 Methods

5.2.1 Literature search

A literature search was performed via the MEDLINE database of English-language, peer-reviewed publications covering the period January 1989 to March 2004. A search for terms "alcohol", "cirrhosis" and either "hepatitis C" or "HCV" in titles, abstracts or key words was used to identify articles, which had examined the association between alcohol use and cirrhosis risk among persons infected with HCV. The references of articles obtained from the MEDLINE search and review papers[229,230,231,232] were also examined for relevant studies.

5.2.2 Criteria for inclusion of articles

Twenty articles, identified through the literature search, were included in the meta-analysis, which fulfilled the following criteria:

(i) study members were infected with chronic HCV, as determined by a positive result in serum from a first-, second- or third-generation enzyme-linked immunosorbent assay and confirmed by means of recombinant immunoblot assay or polymerase chain reaction[233];

(ii) study outcomes included a histopathological diagnosis of cirrhosis (graded based on established scoring systems[234,235,236,237,238,239,240,241]), decompensated cirrhosis (defined clinically by the presence of bleeding oesophageal varices, ascites, hepatic encephalopathy, or hyperbilirubinemia), or advanced fibrosis (which includes both bridging fibrosis with many septa and cirrhosis[237,238,240,241]);

(iii) sufficient information was presented in the article to estimate the relative risk (RR) or odds ratio (OR) of the outcome, and its variance, associated with a category of high compared to low alcohol consumption.

Eighteen articles, which were identified through the literature search and had reported on the alcohol intake and liver disease progression of persons infected with HCV, were excluded from the meta-analysis because either (a) the study outcome included moderate fibrosis[242,243,244,245], (b) the study was confined to patients with minimal or mild chronic hepatitis[246], (c) the study outcome was analysed as a rate of change in fibrosis progression[247,248,249,250], (d) heavy alcohol (defined as at least 280g[251,252] and 350g[253] per week) users were excluded, (e) alcohol had not been analysed in terms of categories[254,255,256,257], or (f) members of the study were included in another article selected (with the most relevant data) for the meta-analysis[258,259].

5.2.3 Extraction of data from articles

The unadjusted and/or adjusted RRs or ORs, with 95% CIs or P values, for the outcome (either cirrhosis, decompensated cirrhosis or advanced fibrosis) associated with categories of alcohol consumption were extracted directly from the article; unadjusted risk ratios were not presented in eleven articles[224,260,261,262,263,264,265,266,267,268,269], but were calculated based on available crude data. Serfaty et al.[270] conducted a case-control study matched for age, gender, route and duration of HCV infection, and the OR for cirrhosis extracted from this article was taken as an adjusted value. Alcohol consumption measures were converted into grams (g) per week (assuming that one unit or drink of alcohol equalled 12g[252]). Three articles[210,263,270] analysed alcohol consumption in terms of more than two categories (e.g. low, medium and high), and the risk estimate used in the meta-analysis from

these studies was the one that had compared the highest with the lowest or baseline category of alcohol intake. Given the reported higher alcohol intake and generally faster HCV disease progression among men compared to women[271,272], it was also of interest to examine the differential risk of severe HCV disease by sex in these studies that had considered the effect of excessive drinking; thus, risk ratios associated with males compared to females were similarly extracted from these articles.

5.2.4 Statistical analyses

To derive pooled risk estimates, the RRs or ORs from each study were first transformed to the natural log scale and the associated variances calculated from either the published 95% CIs or P values[273]. Random- or fixed- effect methods, described by DerSimonian and Laird[274], were used to obtain pooled relative risk estimates from the included studies, dependent on whether the test for heterogeneity (Q-statistic) was or was not significant at the 5% level, respectively[273].

Sensitivity analyses were carried out to examine the effect on the pooled relative risk estimate of the following possible sources of heterogeneity: analysis scale (i.e. odds ratio or relative risk), disease outcome (advanced fibrosis, cirrhosis or decompensated cirrhosis), and threshold for heavy alcohol intake (210-260, 280-504 or 560 grams per week; the middle category included one study which had defined heavy alcohol intake as >280g for women and >420g for men[266]). In addition, weighted linear regression models were performed to determine the significance of the effect of these study characteristics (i.e. analysis scale, disease outcome, and threshold for heavy alcohol intake) on the risk estimate (i.e. log RR or OR), weighted according to the precision of the risk estimate (i.e. inverse of the variance). S-PLUS software was used for all analyses[122,275].

5.3 Results

5.3.1 Characteristics of studies

The characteristics of the twenty articles that fulfilled the inclusion criteria for the meta-analysis are shown in Table 5.1. Thirteen studies were carried out in European countries (one of these also included participants from the United States), three in North America, two in Australia, one in South America and one in Japan. The studies ranged in size from 59 to 5,789 participants and together totalled 15,187 HCV chronically infected individuals. Of this total, 2,716 (18%) had progressed to advanced liver disease, defined as cirrhosis in 13 studies (77%: 2,090/2,716), advanced fibrosis in four studies (19%: 527/2,716), decompensated cirrhosis in two studies (3%: 74/2,716) and cirrhosis/HCC in one (1%; this study involved 20 subjects with cirrhosis only, 4 with both cirrhosis and HCC and one with HCC only[267]).

HCV infection was attributed to injecting drug use and transfusion in 45% and 35%, respectively, of all subjects included in these studies. In the range of 42% to 100%, and overall 64%, of studies' participants were male and their average age at recruitment to the clinic or biopsy ranged between 31 and 61 years (Table 5.1). Six studies[210,264,266,269,270,276] excluded, and one study[277] was confined to, HIV antibody positive individuals. Overall, 15% of 13,181 participants, from studies that reported data, were co-infected with HIV. Of the six studies that reported a prevalence of HIV infection above 5%, all except that by Thomas et al.[263] found a significantly increased risk of severe disease with HIV positivity (Table 5.2).

The threshold for heavy alcohol consumption used in the analyses of these twenty studies ranged from 210g to 560g per week; the latter threshold was the most commonly applied in eight studies, followed by 350g per week used in three studies.

Wiley et al.[266] and Roudot-Thoraval et al.[260] defined different levels of heavy alcohol intake between males (>420g and >504g per week, respectively) and females (>280g and >420g per week, respectively). Uptake of alcohol ranged from only 5% consuming >350g per week in the study by Poynard et al.[276] to 51% consuming >420g and >290g among men and women, respectively, per week by Wiley et al.[266]. An estimated 3,123 HCV chronically infected persons (21% of the total 15,187) were analysed as heavy alcohol users (though heterogeneously defined) in the twenty studies.

5.3.2 Studies' risk estimates of severe HCV disease associated with heavy alcohol consumption

The extracted risk estimates, and confidence intervals, of severe HCV disease associated with the consumption of alcohol from the twenty studies are presented in Table 5.2 (i). The matched case-control study by Serfaty et al.[270] found a raised, but not significant, risk of cirrhosis with >560g of alcohol per week. Adjusted RR estimates of severe disease associated with heavy alcohol intake (defined in the range of at least 240g to 560g per week), presented in the other ten articles, were all significant at the 5% level and ranged from 1.6 to 11.8. Of the remaining nine studies, eight failed to identify a significant association between heavy alcohol consumption (defined in the range of at least 240g to 560g per week) and development of severe HCV disease[210,224,225,226,227,265,268,269]; only unadjusted risk estimates of this association were reported in these nine studies and were included with the adjusted results from the other eleven studies in the following meta-analysis.

5.3.3 Meta-analysis of the risk of severe HCV disease associated with heavy alcohol consumption

The pooled RR estimate of severe disease (i.e. advanced fibrosis, cirrhosis or decompensated cirrhosis) associated with heavy alcohol intake (defined in the range of at least 210 to 560g per week) from the twenty studies was 2.14 (95% CI 1.61-2.85) by the random effects model, as the test for heterogeneity was highly significant ($p<0.0001$). Table 5.3 shows the pooled RR estimates of severe disease associated with heavy alcohol intake according to three possible sources of heterogeneity: analysis scale (i.e. odds ratio or relative risk), disease outcome (advanced fibrosis, cirrhosis or decompensated cirrhosis), and threshold for heavy alcohol intake (210-260, 280-504 or 560 grams per week). The four studies that examined the association between heavy alcohol intake and advanced fibrosis produced the lowest pooled RR estimate (1.63; 95 % CI 1.22-2.17), compared to those studies that examined the risk of cirrhosis (2.14; 1.45-3.17) or decompensated cirrhosis (3.54; 2.14-5.85).

Figure 5.1 shows the individual study risk ratios and pooled RR (2.33; 95% CI 1.67-3.26) from the sixteen studies that examined the association between heavy alcohol intake and development of cirrhosis or decompensated cirrhosis. No difference in risk of cirrhosis or decompensated cirrhosis was found between studies that calculated either relative risks (pooled: 2.31; 95% CI 1.33-4.02) or odds ratios (2.36; 1.52-3.65) (Table 5.3). Surprisingly, the pooled RR estimates for cirrhosis or decompensated cirrhosis decreased with a higher threshold of alcohol intake: 3.54 (95% CI 2.14-5.85), 2.30 (1.18-4.47) and 1.94 (1.26-2.99) with at least 210-260, 280-504 and 560 grams of alcohol per week, respectively. However, the three studies[263,267,278] that used the threshold of 210-260g of alcohol per week had assessed the outcome of decompensated cirrhosis and therefore their relative risk estimates are

not directly comparable with those from the other thirteen studies that examined the outcome of cirrhosis.

5.3.4 Studies' risk estimates of severe HCV disease for men compared to women

Table 5.2 (ii) shows the risk ratios of severe HCV disease for men compared to women extracted from eleven, of the twenty, studies. Serfaty et al.[270] matched for gender in their case-control study and Khan et al.[268] confined theirs to males; thus both were unable to examine the risk of severe disease by this factor. In the remaining seven studies, three[222,260,279] reported no significant difference in prevalence of cirrhosis between men and women, but no data were presented to calculate the risk of severe disease by gender. Seven of the eleven studies, which reported risk ratios, failed to identify a significantly different risk of severe HCV disease between men and women[210,225,226,227,261,266,269]. Unadjusted and adjusted RR point estimates of severe disease for men compared to women (presented in nine and four articles, respectively) ranged from 0.6 to 3.6 and 1.0 to 2.6, respectively. Unadjusted risk ratios associated with gender, from articles that had not presented adjusted estimates, were combined with adjusted results in the following meta-analysis.

5.3.5 Meta-analysis of the risk of severe HCV disease for men compared to women

The pooled RR estimate of severe disease (i.e. advanced fibrosis, cirrhosis or decompensated cirrhosis) for men compared to women from the nine studies was 1.38 (95% CI 1.13-1.69) by the fixed effects model, as the test for heterogeneity was not significant (p=0.1). Table 5.4 shows the RR estimates of severe disease for men compared to women pooled according to the analysis scale and disease outcome used

in studies; results were not pooled in this analysis according to the threshold of heavy alcohol intake applied because only a minority of studies had adjusted gender effect estimates for alcohol consumption. A significantly higher pooled estimate was obtained from studies that calculated relative risks (2.31; 95% CI 1.51-3.52) rather than odds ratios (1.18; 0.94-1.49). The three studies that used the outcome of advanced fibrosis produced a lower pooled estimate (1.13; 95% CI 0.82-1.57) than those studies that examined the risk of cirrhosis (1.39; 1.05-1.84) or decompensated cirrhosis (2.94; 1.53-5.65).

A pooled RR of 1.56 (95% CI 1.21-2.03) for men compared to women was generated from the eight studies that examined the outcome of cirrhosis or decompensated cirrhosis. A higher, but not significantly different, risk of cirrhosis or decompensated cirrhosis was found with the studies that calculated relative risks (pooled: 2.31; 95% CI 1.51-3.52) compared to odds ratios (1.24; 0.89-1.72) (Table 5.4).

5.4 Discussion

In chronic HCV, progression to cirrhosis is almost always the precursor to development of complications such as HCC and liver failure[6]. Thus, determining the factors that accelerate the rate of progression to cirrhosis is a priority for HCV natural history research. Excess alcohol consumption is likely to result in more severe hepatic injury, promoting pathologic progression to cirrhosis among patients with chronic HCV[280]. This meta-analysis estimates the pooled RR of cirrhosis, including decompensated cirrhosis, associated with heavy alcohol intake (defined in the range of at least 210 to 560g per week) to be 2.33 (95% CI 1.67-3.26), derived from sixteen studies involving a total of 13,706 HCV chronically infected persons.

Studies investigating the risk of HCV-related cirrhosis with alcohol involved subjects who had presented to liver clinics, with the exception of those recruited during the Dionysos general population survey[267], and had undergone a liver biopsy. This biased accrual will tend to dampen the estimated regression effect of prognostic indicators as recruited subjects will likely have more advanced liver disease, causing them to present for clinical assessment, and be more prognostically alike than other members of the HCV chronically infected populations where they resided. Moreover, heavy alcohol users could have been under-represented in some studies, as patients consuming alcohol at toxic levels may have been precluded from biopsy[265] and those with histological features of alcoholic hepatitis were excluded from some analyses[265,266]. Such selectivity may have under-estimated the regression effect of alcohol on progression to cirrhosis in the meta-analysis.

The extent of alcohol consumption in these studies is necessarily based on self-reporting, since no other marker is able to establish past intake[231]. Responses could therefore be affected by patients' inability to recall past consumption levels, unwillingness to admit true intake and changes in drinking habits[281]. Questionnaires asking about recent and lifetime alcohol ingestion nevertheless appear to have satisfactory test-retest reliability[282,283,284]. Lifetime alcohol consumption, or that overlapping with duration of HCV infection, has been suggested as the most appropriate measure to assess the dose determining liver damage[180,255]. Most investigators have instead measured alcohol intake over short periods of time, such as during the one to five years prior to HCV diagnosis or histological examination. None of the studies included in the meta-analysis analysed alcohol use as a time-dependent covariate to accommodate the changing behaviour of patients, particularly in response

to medical advice following HCV diagnosis, and explore the impact of curtailed drinking on liver disease progression.

Studies varied widely in their definition of significant alcohol intake, ranging between 210 and 560g per week, and so the true threshold above which alcohol accelerates HCV disease progression remains uncertain[231]. The same levels of intake have been reported with an increased risk of alcoholic liver disease[285]. In a large population-based prospective study of 13,285 individuals, the risk of alcohol-induced liver disease increased significantly from as low as 84-156g per week for women and 168-324g per week for men, and continued to increase with higher levels of alcohol intake[272]. In contrast, the meta-analysis found a slightly lower pooled RR estimate for HCV-related cirrhosis with a higher threshold of alcohol intake: 2.30 (95% CI 1.18-4.47) and 1.94 (1.26-2.99) with at least 280-504 and 560g of alcohol per week, respectively. It is possible that some studies chose the threshold of heavy alcohol use in the range of 280-504g per week during, rather than prior to, the analyses stage as a result of a significant association with cirrhosis; the product of which would have inflated the pooled RR for this group.

Analyses of different endpoints of severe disease have also made it difficult to compare findings on the relationship between alcohol and chronic HCV. The risk of HCV-related disease associated with heavy alcohol intake increased with the severity of the outcome: the lowest (1.63; 95% CI 1.22-2.17) and highest (3.54; 2.14-5.85) pooled RR estimates were obtained for advanced fibrosis and decompensated cirrhosis, respectively.

Chronic HCV has been shown to be histologically milder in women than men[276]. Wiley et al.[266] indicated that the difference in risk of HCV-related cirrhosis between the sexes could be explained by the higher consumption of alcohol among

men compared to women. A complicating factor is that there is also evidence to suggest that women may be more susceptible to the adverse effects of alcohol at lower levels of consumption than men. The population-based Dionysos study found the risk of cirrhosis was twice as high in women as in men with the same amount of alcohol intake[286]. Poynard et al.[276] and Harris et al.[278] both reported a significantly increased risk of HCV-related severe disease (cirrhosis and decompensated cirrhosis, respectively) for men compared to women (risk ratios: 2.0, 95% CI 1.2-3.3; and 2.6, 1.1-5.9, respectively), after adjustment for heavy alcohol intake (defined as >350 and ≥240g per week, respectively) and other factors. Overall, a lower RR estimate (1.56, 95% CI 1.21-2.03) comparing men to women was obtained from the eight studies that examined, in either unadjusted or adjusted analyses, the outcomes of cirrhosis and decompensated cirrhosis. Unfortunately, only three[266,276,278] of these eight studies presented risk estimates of HCV-related cirrhosis by gender from multi-factorial analyses, and so it was not possible to fully assess if the raised risk for males diminished after adjusting for the influence of heavy alcohol use.

In conclusion, studying the relationship between HCV and alcohol is inherently problematic because of difficulties in obtaining an accurate history of alcohol use and clinic-recruitment biases. The role of alcohol in HCV-related cirrhosis may therefore be under-estimated. Nevertheless, the evidence overwhelmingly shows a worsened outcome for those with chronic HCV and concurrent alcohol use. The amount of alcohol that can be safely consumed by patients with HCV is unclear; published data show that even moderate intake can increase the severity of liver disease[231]. Alcohol consumption should be minimised as much as possible in those who have chronic HCV until a safe threshold is more definitively determined.

Table 5.1: Characteristics of the twenty studies included in the meta-analysis relating to the impact of alcohol use on HCV-induced liver disease.

First author, Year published	Country	Study selection criteria	N	Outcome n (% of N)	Risk group % of N	Male % of N	Age at recruitment to clinic or biopsy Mean (years)	HIV co-infection % of N	Heavy alcohol consumption	
									Definition (g per week) [time period]	n (% of N)
Strasser, 1995[224]	Australia	Consecutive patients referred to liver clinic	152	Cirrhosis 49 (32%)	51% IDU, 15% transfusion, 6% tattoo only, 28% sporadic*	63%*	Median of 53 among cirrhotics and 33 among non-cirrhotics	NS	≥ 420 [-]	76 (50%)
Serfaty, 1997[270]	France	Case-control study of patients admitted to hospital; HIV-ve; HBsAg-ve; untreated for HCV	168	Cirrhosis 84 (50%)	12% IDU, 51% transfusion, 37% sporadic	64%	54 among both cases and controls	0%	≥ 560 [last 5 years]	21 (13%)
Roudot-Thoraval, 1997[260]	France	Patients with elevated ALT levels; HCV treatment involved	5,789	Cirrhosis 1,237 (21%)	23% IDU, 37% blood product, 15% nosocomial, 3% occupational, 1% sexual, 20% not known*	59%*	45*	5%	>420 for women & >504 for men [at least 1 year]	1,222 (18%)
Verbaan, 1998[261]	Sweden	Consecutive patients referred to liver clinic; untreated for HCV	99	Cirrhosis 20 (20%)	59% IDU, 18% transfusion, 23% not known*	75%	49 among cirrhotics and 41 among non-cirrhotics	NS	≥ 560 [at least 5 years]	45 (45%)
Pol, 1998a[222]	France	Patients with histological evaluation before HCV therapy; date of infection known; HBsAg-ve; parenterally acquired HCV	553	Cirrhosis 69 (12%)	46% IDU, 54% transfusion*	67%*	39*	9%	≥ 560 [at least 2 years]	97 (18%)*
Pol, 1998b[262]	France	Patients with a history of injecting drug use; HCV treatment involved	210	Cirrhosis 41 (20%)	100% IDU	76%	33	29%	> 560 [at least 2 years]	76 (36%)
Khan, 1998[265]	Australia	Patients referred to liver clinic; those with hepatitis B excluded.	434	Cirrhosis 88 (20%)	45% IDU, 26% transfusion, 6% tattoo, 4% other, 19% sporadic.	66%	41	NS	> 560 [at least 5 years]	104 (24%)
Wiley, 1998[266]	USA	Patients referred to liver clinic; those with hepatitis B, HIV, other liver diseases, renal failure, HCV therapy excluded	176	Cirrhosis 69 (39%)	56% IDU, 44% transfusion	62%	46	0%	>280 for women & >420 for men [at least 5 years]	90 (51%)
Bellentani, 1999[267]	Italy	Participants of a general population survey.	162	Cirrhosis/HCC 25 (15%)	2% IDU, 15% transfusion, 83% not known*	42%*	81% aged 46-65	NS	> 210 [-]	36 (22%)
Khan, 2000[268]	Japan	Patients referred to liver clinic; those with hepatitis B, other liver diseases, HCV therapy excluded	106	Cirrhosis 54 (51%)	0% IDU, 100% transfusion	100%	60	NS	> 560 [at least 5 years]	24 (23%)
Loguercio, 2000[269]	Italy	Patients referred to liver clinic; those with hepatitis B, HIV, other liver diseases, HCV therapy excluded.	164	Cirrhosis 70 (43%)	0% IDU, 13% transfusion, 87% sporadic*	60%	Median of 61 among cirrhotics and 49 among non-cirrhotics	0%	> 560 [at least 5 years]	35 (21%)
Thomas, 2000[263]	USA	IDUs participating in a cohort study; age >17 years; only 1 case treated for HCV	1,667	Decompensated cirrhosis 40 (2%)	100% IDU	78%	34	33%	> 260 [average for follow-up]	496 (30%)
Poynard, 2001[276]	France & USA	Patients with no other liver disease or HCC; date of infection known; HbsAg-ve; HIV-ve; untreated for HCV	2,313	Cirrhosis 205 (9%)	50% IDU, 50% transfusion	60%	43	0%	> 350 [-]	115 (5%)
Di Martino, 2001[225]	France	Patients with a history of injecting drug use; not coinfected with hepatitis B and delta virus; HCV treatment involved	160	Cirrhosis 20 (13%)	100% IDU	73%	31	50%	> 560 [past 5 years]	34 (21%)

* Estimated from available data in article; NS Not stated in article; USA United States of America.

(Table 5.1 continued over page)

Table 5.1 (continued): Characteristics of the twenty studies included in the meta-analysis relating to the impact of alcohol use on HCV-induced liver disease.

First author, Year published	Country	Study selection criteria	N	Outcome n (% of N)	Risk group % of N	Male % of N	Age at recruitment to clinic or biopsy Mean (years)	HIV co-infection % of N	Heavy alcohol consumption	
									Definition (g per week) [time period]	n (% of N)
Harris, 2002[223]	UK	Cohort of transfusion recipients traced during an HCV look-back programme; HCV treatment involved	755	Decompensated cirrhosis 34 (5%)	100% transfusion	48%*	55*	NS	≥ 240 [current]	102 (14%)*
Costa, 2002[226]	Brazil	Patients with parenterally acquired HCV; date of infection known; those with HBV, HIV, renal failure or previous HCV treatment were excluded	59	Advanced fibrosis 23 (39%)	27% IDU, 73% transfusion	73%	43	0%	> 350 [-]	22 (37%)
Mohsen, 2003[227]	UK	Patients with known date of infection; HBsAg-ve; absence of other liver diseases; untreated for HCV	208	Advanced fibrosis 74 (36%)	77% IDU, 23% transfusion	72%	Median 39	26%	> 240 [current]	37 (18%)
Serra, 2003[279]	Spain	Spanish patients with liver biopsy	298	Advanced fibrosis 110 (37%)	30% IDU, 62% transfusion, 8% other*	52%	46*	NS	> 420 [-]	47 (16%)
Martin-Carbonero, 2004[277]	Spain, Italy, France & Germany	HIV+ve patients; elevated ALT levels; HBsAg-ve; absence of other liver diseases; untreated for HCV	914	Advanced fibrosis 320 (35%)	83% IDU, 5% transfusion, 12% sexual activity	75%	Median 37	100%	> 350 [at least1 year]	214 (23%)
Monto, 2004[210]	USA	Liver biopsy patients; HIV-ve; absence of other liver diseases; untreated for HCV	800	Cirrhosis 84 (11%)	63% IDU, 18% transfusion, 19% not known*	77%	48*	0%	> 350[¶] [drinking career]	230 (29%)

* Estimated from available data in article; NS Not stated in article; UK United Kingdom; USA United States of America; [¶] Defined as > 413g/week in analyses (Table 5.2).

Table 5.2: Risk of severe disease (i.e. cirrhosis, decompensated cirrhosis or advanced fibrosis) associated with (i) alcohol consumption and (ii) gender reported among twenty studies of HCV chronically infected persons included in the meta-analysis.

First author, Year published	Outcome in analyses	(i) Alcohol consumption			(ii) Gender (males compared to females)		Other covariates included in adjusted model
		Definition (g per week) [time period]	Risk Ratio (95% CI)		Risk Ratio (95% CI)		
			Unadjusted	Adjusted	Unadjusted	Adjusted	
Strasser, 1995[224]	OR of cirrhosis	< 420 ≥ 420 [-]	Baseline 0.51 (0.24-1.08)	-	-	-	Age*
Serfaty, 1997[270]	OR of cirrhosis	< 560 ≥ 560 [last 5 years]	-	Baseline 1.74 (0.63-4.92)	-	-	Matched for age, sex, route and duration of infection
Roudot-Thoraval, 1997[260]	OR of cirrhosis	< Excessive Excessive (i.e. > 420 (women) or 504 (men)) [at least 1 year]	Baseline 2.41 (2.08-2.80)*	Baseline 3.38 (2.82-4.05)*	-	-	Route of infection*, HBsAg +ve*, Age*
Verbaan, 1998[261]	OR of cirrhosis	< 560 ≥ 560 [at least 5 years]	Baseline 1.26 (0.47-3.35)	Baseline 11.80 (1.90-72.1)*	0.55 (0.19-1.58)	-	Immigrant*, Duration of infection, HCV genotype, HBcAb, Low plasma α_1 ACT level*, Age*
Pol, 1998a[222]	RR of cirrhosis	< 560 ≥ 560 [at least 2 years]	-	Baseline 2.90 (1.60-5.40)*	-	-	Sex, Duration of infection*, HIV+ve*, kidney recipient, Age at infection*
Pol, 1998b[262]	RR of cirrhosis	≤ 560 > 560 [at least 2 years]	Baseline 1.60 (0.94-2.72)	Baseline 1.90 (1.00-3.90)*	-	-	HIV +ve*
Khan, 1998[265]	RR of cirrhosis	≤ 560 > 560 [at least 5 years]	Baseline 0.93 (0.59-1.49)	-	-	-	-
Wiley, 1998[266]	OR of cirrhosis	< Excessive Excessive (i.e. > 280 (women) or 420 (men)) [at least 5 years]	Baseline 4.41 (2.29-8.50)†*	Baseline 4.37 (2.17-8.83)†*	1.72 (0.91-3.26)†	1.02 (0.50-2.10)†	-
Bellentani, 1999[267]	OR of cirrhosis/HCC	≤ 210 > 210 [-]	Baseline 4.35 (1.62-11.74)*	-	-	-	-
Khan, 2000[268]	OR of cirrhosis	≤ 560 > 560 [at least 5 years]	Baseline 2.32 (0.82-6.71)	-	-	-	-
Loguercio, 2000[269]	OR of cirrhosis	≤ 560 > 560 [at least 5 years]	Baseline 1.57 (0.69-3.55)	-	0.88 (0.44-1.73)	-	-
Thomas, 2000[263]	RR of decompensated cirrhosis	< 90 90-260 > 260 [average for follow-up]	Baseline 1.53 (0.63-3.68) 3.66 (1.75-7.63)*	Baseline 1.57 (0.65-3.79) 3.60 (1.73-7.52)*	3.57 (1.22-10.43)¶*	-	Age at infection*
Poynard, 2001[276]	RR of cirrhosis	≤ 350 > 350 [-]	-	Baseline 4.50 (1.73-11.68)¶*	-	2.00 (1.22-3.28)¶*	Route of infection, Histological activity index (HAI), Age at infection*
Di Martino, 2001[225]	RR of cirrhosis	≤ 560 > 560 [past 5 years]	Baseline 2.65 (0.62-11.32)	-	3.22 (0.91-11.34)	-	Interferon therapy*, CD4 count*, Age at infection*

OR Odds Ratio; RR Relative risk; * Significant at the 5% level; ¶ 95% confidence interval (CI) derived from the reported P-value; † Derived from crude data reported in article; - Data missing or factor not included in analysis.

(Table 5.2 continued over page)

Table 5.2 (continued): Risk of severe disease (i.e. cirrhosis, decompensated cirrhosis or advanced fibrosis) associated with (i) alcohol consumption and (ii) gender reported among twenty studies of HCV chronically infected persons included in the meta-analysis.

First author, Year published	Outcome in analyses	(i) Alcohol consumption			(ii) Gender (males compared to females)		Other covariates included in adjusted model
		Definition (g per week) [time period]	Risk Ratio (95% CI)		Risk Ratio (95% CI)		
			Unadjusted	Unadjusted	Unadjusted	Adjusted	
Harris, 2002[223]	OR of decompensated cirrhosis	1-239 ≥ 240 [current]	-	Baseline 2.84 (1.09-7.41)*	-	2.63 (1.14-5.88)*	Duration of infection, HCV ribonucleic acid status, Smoking status
Costa, 2002[226]	OR of advanced fibrosis	≤ 350 > 350 [-]	Baseline 0.84 (0.24-2.84)	-	0.76 (0.20-2.85)	-	Duration of infection*, Age at infection*
Mohsen, 2003[227]	OR of advanced fibrosis	≤ 240 > 240 [current]	Baseline 1.31 (0.77-2.65)	-	0.93 (0.50-1.86)	-	HIV positivity*, Duration of infection*, ALT*
Serra, 2003[279]	OR of advanced fibrosis	≤ 420 > 420 [-]	-	Baseline 2.86 (1.39-5.90)*	-	-	Age at diagnosis*
Martin-Carbonero, 2004[277]	OR of advanced fibrosis	≤ 350 > 350 [at least1 year]	Baseline 1.88 (1.31-2.69)*	Baseline 1.61 (1.10-2.35)*	1.77 (1.25-2.56)*	1.26 (0.94-2.06)	CD4 count*, Age*
Monto, 2004[210]	OR of cirrhosis	< 25.2 25.2-121.1 121.1-413 > 413 [drinking career]	Baseline 0.87 (0.43-1.76) 1.06 (0.54-2.08) 1.84 (0.99-3.42)	-	1.59 (0.88-2.90)	-	-

OR Odds Ratio; RR Relative risk; * Significant at the 5% level; ¶ 95% confidence interval (CI) derived from the reported P-value; - Data missing or factor not included in analysis.

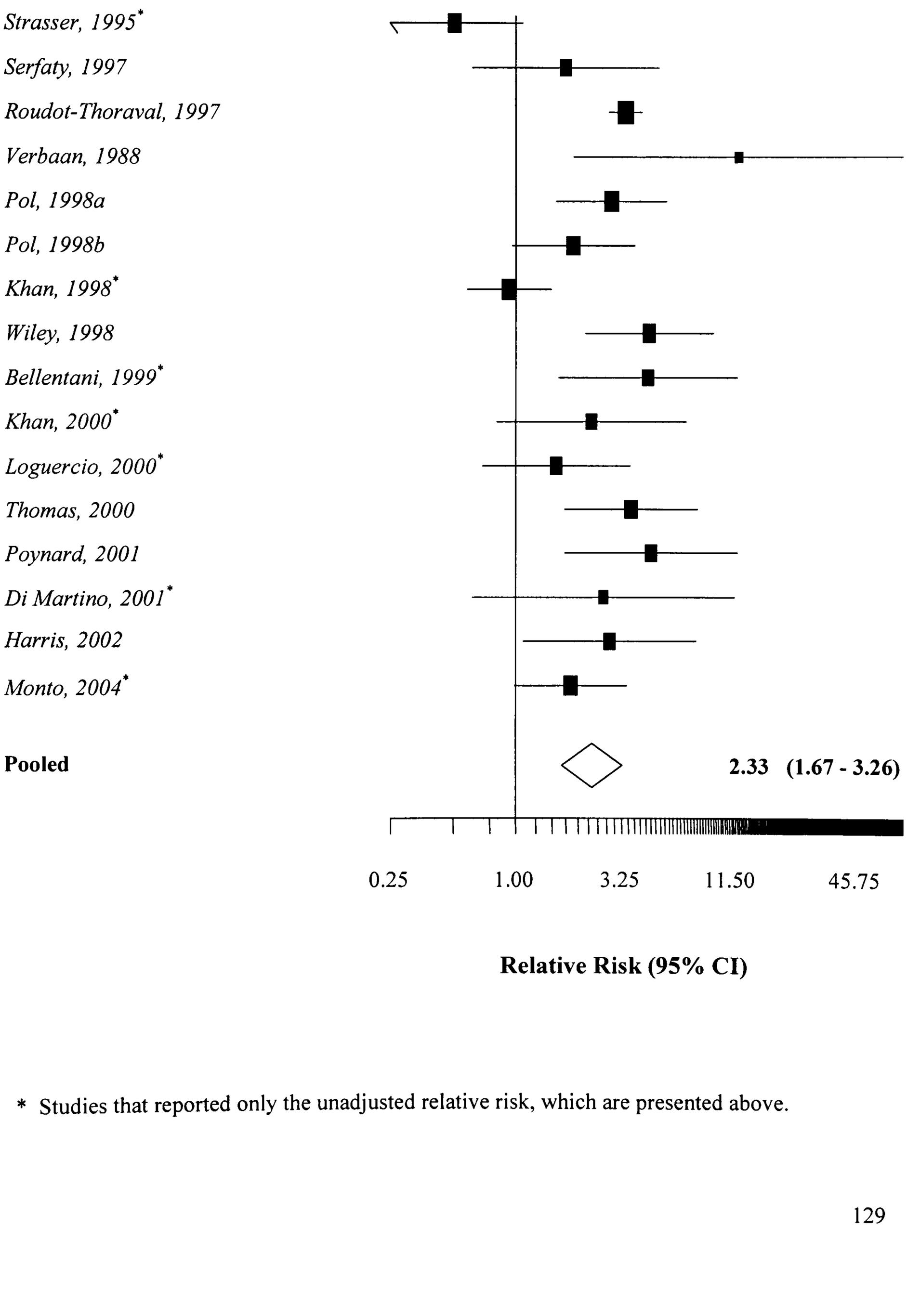
Table 5.3: Pooled[¶] relative risk estimates of the outcome (advanced fibrosis, cirrhosis or decompensated cirrhosis) associated with heavy alcohol intake compared to less than heavy alcohol intake among HCV chronically infected patients: results of a meta-analysis.

Study characteristics		Number of studies	Pooled Relative Risk[¶] (95% CI)	Heterogeneity Q-statistic (P-value)	Significance of characteristic: P-value
ALL STUDIES					
Total		20	2.14 (1.61-2.85)	70.1 (<0.0001)	-
Analysis scale	Odds ratio	14	2.08 (1.48-2.94)	49.3 (<0.0001)	Baseline
	Relative risk	6	2.31 (1.33-4.02)	17.2 (0.004)	0.34
Outcome	Advanced fibrosis	4	1.63 (1.22-2.17)	3.9 (0.3)	0.14
	Cirrhosis	13	2.14 (1.45-3.17)	55.3 (<0.0001)	Baseline
	Decompensated cirrhosis	3*	3.54 (2.14-5.85)	0.4 (0.8)	0.54
Threshold for heavy alcohol intake (g/week)	210-260	4	2.38 (1.61-3.52)	6.4 (0.1)	Baseline
	280-504	8	2.07 (1.30-3.30)	39.7 (<0.0001)	0.75
	560	8	1.94 (1.26-2.99)	14.7 (0.04)	0.46
STUDIES WHICH ANALYSED OUTCOMES: COMPENSATED AND DECOMPENSATED CIRRHOSIS					
Total		16	2.33 (1.67-3.26)	57.0 (<0.0001)	-
Analysis scale	Odds ratio	10	2.36 (1.52-3.65)	32.9 (<0.0001)	Baseline
	Relative risk	6	2.31 (1.33-4.02)	17.2 (0.004)	0.19
Threshold for heavy alcohol intake (g/week)	210-260	3	3.54 (2.14-5.85)	0.4 (0.8)	Baseline
	280-504	5	2.30 (1.18-4.47)	27.2 (<0.0001)	0.76
	560	8	1.94 (1.26-2.99)	14.7 (0.04)	0.18

[¶] Pooled estimate was derived using random or fixed effects methods according to whether the test for heterogeneity was significant at the 5% level or not, respectively.

* Included the study by Bellentani et al.[287] that analysed the combined outcome of cirrhosis and HCC.

Figure 5.1: Individual study adjusted* and pooled relative risk estimates of cirrhosis associated with heavy alcohol intake compared to less than heavy alcohol intake among HCV chronically infected patients: results of meta-analysis (excludes four studies which estimated the risk for advanced fibrosis).



* Studies that reported only the unadjusted relative risk, which are presented above.

Table 5.4: Pooled[¶] relative risk estimates of the outcome (advanced fibrosis, cirrhosis or decompensated cirrhosis) associated with male compared to female HCV chronically infected patients: results of a meta-analysis.

Study characteristics		Number of studies	Pooled Relative Risk[¶] (95% CI)	Heterogeneity Q-statistic (P-value)	Significance of characteristic: P-value
ALL STUDIES					
Total		11	1.38 (1.13-1.69)	17.1 (0.1)	-
Analysis scale	Odds ratio	8	1.18 (0.94-1.49)	8.5 (0.3)	Baseline
	Relative risk	3	2.31 (1.51-3.52)	1.2 (0.5)	0.03
Outcome	Advanced fibrosis	3	1.13 (0.82-1.57)	1.0 (0.6)	0.45
	Cirrhosis	6	1.39 (1.05-1.84)	9.4 (0.1)	Baseline
	Decompensated cirrhosis	2	2.94 (1.53-5.65)	0.2 (0.7)	0.11
STUDIES WHICH ANALYSED OUTCOMES: COMPENSATED & DECOMPENSATED CIRRHOSIS					
Total		8	1.56 (1.21-2.03)	13.9 (0.1)	-
Analysis scale	Odds ratio	5	1.24 (0.89-1.72)	7.4 (0.1)	Baseline
	Relative risk	3	2.31 (1.51-3.52)	1.2 (0.5)	0.11

[¶] Pooled estimate was derived using random or fixed effects methods according to whether the test for heterogeneity was significant at the 5% level or not, respectively.

Chapter 6: Modelling the current and future disease burden of hepatitis C among injecting drug users in Scotland

6.1 Introduction

Hepatitis C virus (HCV) is a slowly progressive disease: a systematic review of the worldwide literature indicated that 4%-10% of those with active viraemia develop cirrhosis after twenty years of infection[94]. Studies have demonstrated considerable variability in rates of HCV disease progression because of the biased selection of cohorts with respect to disease stage and host characteristics. Factors most commonly shown to accelerate natural history include alcohol, co-infection with HIV, older age at HCV acquisition and male gender[288].

In most resource-rich countries, the majority of those with HCV acquired their infection in the late 1970s and 1980s[167], before the identification of the virus and the availability of diagnostic tests. Given that chronic HCV does not result in major morbidity for many years, the impact of this infection on health care systems is only now becoming apparent. For example, HCV has become the leading cause of liver transplantation in the United States[15]. There are also concerns over the burgeoning medical costs of treating chronic HCV. In 2001, UK consensus guidelines on the clinical management of HCV infection recommended that antiviral treatment should be offered to patients without contraindications such as continued injecting who were shown to have moderate disease according to histological appearances[289]. Persons who are HCV seropositive but who are otherwise healthy are likely to represent a growing number of candidates for treatment.

In Scotland, a total of 14,390 persons had been diagnosed with HCV antibodies by the end of June 2002[21]. Among those for whom at least one risk factor

was known, almost 90% (8719/9728) had injected drugs, 6% (584/9728) had received blood or blood products and 4% reported occupational needlestick injuries, tattoos, body piercings or sexual contact. By the end of 2000, less than 10% of HCV diagnosed persons in Scotland had, however, received antiviral therapy[52] and a further 70-80% of the total HCV infected female population remained undiagnosed[53]. To plan an appropriate public health response to this HCV epidemic, in terms of both treatment needs and preventive measures, quantitative estimates of the current and future burden of HCV disease are required.

In this chapter, the objectives were to develop a comprehensive model to estimate the numbers of, both current and former, injecting drug users (IDUs) in Greater Glasgow and Scotland belonging to different stages of HCV disease now and in the future. Modelling was confined to the IDU population because much of the epidemiological data available to date and the overwhelming majority of HCV transmissions in Scotland have been associated with this risk group. To determine the benefit of treating HCV chronically infected patients, the impact of different antiviral treatment strategies on the incidence of severe HCV-related disease was explored.

6.2 Aims

The primary aims were to develop a model to estimate:

(i) the number of IDUs (categorised according to current and former status) who acquired HCV infection and progressed to mild, moderate and severe HCV disease in Glasgow and Scotland between 1960 and 2030;

(ii) the number of cases of severe HCV-related disease (i.e. decompensated cirrhosis and HCC) among IDUs that could be prevented in the future through a range of antiviral treatment strategies.

6.3 Methods

6.3.1 Overview

The study involved three stages: (a) the development of an HCV disease progression model for the IDU population in Greater Glasgow (a region which has approximately a third of all IDUs in Scotland[108] and a wealth of epidemiological data); (b) using the model developed in (a), a comparison of the impact of different antiviral treatment scenarios on severe sequelae of HCV infection; and (c) the extension of the model developed for Greater Glasgow in (a) to the entire Scottish IDU population.

The progression model (a) was designed to incorporate both the knowledge and uncertainty about major parameters relating to (i) the IDU population (i.e. incidence and cessation of injecting and mortality), (ii) the characteristics of the IDU population affecting HCV progression (i.e. gender, age, co-infection with HIV and heavy alcohol intake), (iii) the incidence of HCV infection among current IDUs, and (iv) the rate of HCV disease progression (including the influence of host factors and the current uptake of antiviral therapy). Local data were used to inform parameters (i), (ii) and (iii), available up to 2000 (estimates from this year were applied in subsequent years, 2001-2030), and the world-wide literature was reviewed to inform on (iv). Modelled outcomes were fitted to available epidemiological data on the prevalent number of current IDUs, the prevalence of HCV infection among current IDUs, and the incident number of HCV-related decompensated cirrhosis cases among IDUs.

6.3.2 Model structure

In annual cycles between 1960 and 2030, Markov modelling was used to simulate individuals' progression from commencement of injecting drug use through

predefined HCV disease states until death (Figure 6.1). Progression annually from one state to another was based on transition probabilities derived from a comprehensive review of the literature (described below). The model distinguishes between HCV uninfected, chronically infected, and previously, but no longer, infected persons. Once chronically infected, cases had the potential to progress sequentially to moderate disease, compensated cirrhosis, and then either decompensated cirrhosis or HCC. For example, each year, former IDUs with mild chronic HCV infection could either develop moderate disease, remain stable with mild disease or die from causes unrelated to HCV. Transplantation was also a possibility for decompensated cirrhosis cases.

Persons belonging to the group with moderate disease benefit most cost-effectively[54] from, and should therefore be offered, antiviral therapy as recommended by the Royal College of Physicians of London and the British Society of Gastroenterology[289] (i.e. those with histological appearances of 3-5/6 on fibrosis score and/or > 3/18 on necroinflammatory score[240]). In the model, persons were further characterised according to age, gender, heavy alcohol use and co-infection with HIV (described below) to explore the influence of these factors on progression from chronic HCV infection to cirrhosis. Persons exit the model upon death from causes unrelated (specified separately for current and former IDUs) and related to HCV (i.e. decompensated cirrhosis, HCC and post-transplantation). By tracking individuals' development of HCV-related complications each year, during 1960-2030, the model estimates past, current and future HCV-related morbidity and mortality. The software used to generate simulations was SPLUS[122].

6.3.3 Model parameters

6.3.3.1 The IDU population: incidence and cessation of injecting and mortality

Estimates of the incidence and cessation of injecting and mortality among current IDUs, each calendar year between 1960 and 2000 in Glasgow, were derived through the use of (i) a modified Delphi approach, which combined expert opinion with capture-recapture IDU prevalence estimates (Figure 3.1), and (ii) an annual rate of mortality, from overdose and other causes (unrelated to HCV and HIV), in the range of 1-2%[123,124,290,291]. In the HCV progression model, current IDUs were assumed to have ceased injecting by 50 years of age, because individuals newly attending drug services in Glasgow, who report injecting in the past month, were almost all aged under 50 years (99.9% of 8,362 during years 1995-2001; Scottish Drug Misuse Database, ISD, Edinburgh). The annual mortality of former IDUs from causes unrelated to HCV and HIV was also accounted for, and assumed to be two to five times higher[83,292] than the average annual age- and gender-specific rates for the general Scottish population[293].

6.3.3.2 The characteristics of the IDU population affecting HCV progression

6.3.3.2.1 *Gender and age*

The gender and age distributions of newly initiated IDUs were based on those reported among representative samples of current IDUs surveyed in Glasgow during the 1990s[110]: 27.5% (standard deviation of 2.5%) were assumed to be female (generated according to the normal distribution) and the mean age at commencement of injecting was assumed to be 17.5 years up until the mid 1980s, increasing linearly thereafter to 23.5 years by 2000 (generated according to the lognormal distribution, with a standard deviation on the logarithm scale of 0.2).

6.3.3.2.2 *Co-infection with HIV*

The majority of HIV infections among IDUs in Scotland occurred during 1983-85 (an estimated 1,000 of whom only 15% resided in the Greater Glasgow area[294]). Mortality among HIV infected IDUs was based on data generated by the Collaborative Group on AIDS Incubation and HIV Survival[295], and adjusted down (i.e. hazard rate reduced by 75%) for the period after 1995 to allow for increased survival due to the impact of Highly Active Anti-Retroviral Therapy.

6.3.3.2.3 *Heavy alcohol use*

Heavy alcohol intake, such as that above 50g per day (or 350g per week), increases the rate of liver disease progression in the HCV chronically infected person[95,210]; some, but not all, studies have found even lower thresholds to be associated with an increased rate of progression[270,263]. Alcohol consumption among current and former IDUs in Scotland, however, has not been well studied. Studies of drug users receiving drug treatment in England have reported prevalences in the range of 15-45%[218,219,296,297] for either problem drinking or drinking above the recommended safe limits of 14 units (168g) per week for women and 21 units (252g) for men; further, no change in alcohol intake was detected among 276 opiate users pre and post initiation to methadone treatment[298]. To accommodate this range of uncertainty, three rates (0%, 20% and 40%) of heavy alcohol use were explored in the HCV projection model.

6.3.3.3 The incidence of HCV infection among current IDUs

Estimates of the percentage of (i) uninfected current IDUs who acquired HCV and did not clear their infection (i.e. chronic infection), (ii) uninfected current IDUs who acquired HCV and spontaneously cleared their infection, and (iii) previously infected (but cleared their infection) current IDUs who were re-infected with HCV and did not clear their re-infection (i.e. chronic infection), each calendar year between 1960 and 2000 in Glasgow, were generated (Figure 3.7). Briefly, stochastic simulation had been used to model the transmission of HCV according to the needle/syringe sharing behaviours of current IDUs in Glasgow and the characteristics (i.e. transmissibility and chronicity) of HCV infection; of note, 15-40% of current IDUs with newly acquired HCV were assumed to recover from their acute infection spontaneously[3,4] and become susceptible to re-infection with HCV. Only those estimates of (i), (ii) and (iii) which provided modelled estimates of HCV seroprevalence consistent with survey data, obtained through community-wide studies of Glasgow IDUs between 1990 and 1999[47], were used in the projection model (Chapter 3, Figure 3.6; 85% of 1000 simulation runs were consistent with survey data). Model parameter values for the year 2000 were applied in subsequent years up to 2030. Given the slow course of HCV disease progression, cases newly infected in 2001-2030 would not impact greatly on the estimated burden of severe disease during this period.

6.3.3.4 The rate of HCV disease progression

In the progression model, individuals infected with chronic HCV were followed through a series of disease states, as shown in Figure 6.1. The transition rates, by which individuals progress from one disease state to another, were obtained through a review of the literature (described below).

6.3.3.4.1 *Chronic HCV to moderate disease and compensated cirrhosis*

Progression from chronic HCV to compensated cirrhosis was modelled based on a Weibull distribution with cirrhosis prevalence estimated at 6.5% (95% CI 3.5-9.5%) and 20% (10-40%) after 20 and 40 years, respectively, according to a recent systematic review of nine community-based studies[94,95]. Progression from chronic HCV to moderate disease (defined as 3-5/6 on fibrosis stage and/or >3/18 on necroinflammation grade[240]), similarly, was estimated from these community-based studies (except that only three of the nine studies reported relevant data, Table 6.1). An estimated 56% (43-70%) of chronically infected cases had moderate disease after 20 years.

An increased rate of progression to cirrhosis among chronically HCV infected individuals who were (i) male (relative risk 1.56, 95% CI 1.21-2.03; Chapter 5), (ii) older at HCV acquisition (1.08 per year, 1.04-1.12)[299], (iii) co-infected with HIV (2.92, 1.70-5.01)[221], and (iv) heavy alcohol users (2.33, 1.67-3.26; Chapter 5) was also explored in the model. The assumed risks of cirrhosis at 20 and 30 years following chronic infection according to these characteristics are detailed in Table 6.2.

6.3.3.4.2 *Compensated cirrhosis to decompensated cirrhosis, HCC and death*

The transition rates of HCV chronically infected persons following the development of compensated cirrhosis are detailed in Table 6.3 and referred to as transitions (i)-(vii). The annual probability of liver transplantation (iii) among decompensated cirrhosis cases was based on the Scottish data presented in Chapter 4.4.6. For the remaining transition rates, pertinent English-language papers were identified through the PubMed database which was searched to the end of January 2004 using the terms

"hepatitis C" and either "cirrhosis", "hepatocellular carcinoma" or "liver transplantation", and augmented by additional citations from these papers.

Quantitative data were extracted from each paper on (A) the cumulative probability (*s(t)*) of not progressing to the outcome (or who had survived) at *t* years (*t*=5 for transitions (i), (ii), (iv), (vii); *t*=2 for (v); *t*=1 for (vi)); (B) the total number of subjects (*n*); and (C) the number (or estimate of the number) of subjects censored (*c(t)*) prior to *t* years; probabilities *s(t)* were converted into average annual progression rates (i.e. $1\text{-}s(t)^{1/t}$) and are presented in Table 6.3. Pooled estimates (with 95% CIs) of *s(t)* were derived using random effects[273,275], where the variance of *s(t)* was estimated using Peto's method[300] (i.e. $s(t)(1\text{-}s(t))/(n\text{-}c(t))$), and then converted into annual progression rates as above; the 95% CI ranges of the pooled annual progression rates were used in the model (Table 6.3).

6.3.3.4.3 *Current uptake of antiviral therapy*

The model was also designed to take account of chronically HCV infected former IDUs' (with moderate disease) initiation on, and response to, antiviral therapy. Other factors influencing eligibility for treatment in clinical practice (e.g. heavy alcohol use, HIV co-infection and psychiatric status) were not considered. Clearance of the virus was estimated at 20%, 40% and 50% with interferon alone, interferon plus ribavirin and pegylated interferon plus ribavirin, respectively[301,302,8]. Compliance to HCV treatment once initiated was assumed to be 90%[303,304]. Re-treatment of non-responders to initial course of antiviral therapy was not considered in the model. The number of IDUs who had been initiated on antiviral therapy in Scotland by the end of 2003 was estimated, optimistically, at 1,500 based on limited data[52]; a third were assumed to reside in Greater Glasgow and 25%, 30% and 45% were assumed to have received

treatment during 1993-97 (with interferon alone), 1998-2000 (with interferon plus ribavirin) and 2001-03 (with interferon plus pegylated interferon), respectively. Uptake of treatment in subsequent years was set the same as in 2003; different uptake rates were also applied to assess the potential of antiviral therapy to reduce the incidence of severe HCV disease in the future (described below).

6.3.4 Model fitting

The aim of the model fitting process was to assess the validity of model assumptions – in particular, progression to compensated cirrhosis and the influence of host factors (Table 6.2) – to generate outcomes consistent with available epidemiological data. Each simulation generated estimates of the number of new decompensated cirrhosis cases per year (S_i) which were compared with the expected number determined through record-linkage (R_i), for years 1996-2001 (Table 4.6), using a standard χ^2 goodness-of-fit measure. If the goodness-of-fit test statistic $\left(\sum_{i=1996}^{2001} \frac{(S_i - R_i)^2}{R_i} \right)$ was less than 20.52, the 99.9% critical value for the χ^2 distribution on 5 degrees of freedom, the simulated data were regarded as consistent with the record-linkage data; the 99.9%, instead of 95% (i.e. 11.07), critical value was chosen to allow for uncertainty in the number of cases derived through record-linkage. Simulations were performed until 1,000 accumulated which produced simulated results consistent with record-linkage data by this criterion.

6.3.5 Different antiviral treatment scenarios

The number of HCV chronically infected former IDUs initiated on antiviral therapy in Glasgow in 2005, and in each year thereafter, was increased from the estimated

current uptake of 75 to a range of maxima of 250, 500, and 1,000 per year. The stage of chronic HCV disease at which former IDUs were initiated on treatment was varied between (i) moderate disease only, (ii) a combination of moderate disease and compensated cirrhosis, and (iii) a combination of mild disease and moderate disease; the response to antiviral therapy was assumed the same irrespective of the stage of chronic HCV disease. The number of severe HCV-related events (i.e. decompensated cirrhosis and HCC) potentially prevented among IDUs in Glasgow as a result of the above different treatment scenarios during 2005-30 was estimated.

6.3.6 Extension of model to the entire Scottish IDU population

The model developed for Glasgow was adapted to the whole of Scotland, based on available epidemiological data, by adjusting four key parameters. First, the number of individuals who commenced injecting each calendar year was increased (2-fold that used for Glasgow by 1980, increasing to 3-fold by 1990 and 4-fold by the mid-1990s) in accordance with data on the prevalence of current IDUs in Scotland[100,108]. Secondly, the percentage of current IDUs who acquired HCV infection each calendar year was halved for Scotland compared to that for Glasgow in 1987 onwards, in accordance with HCV seroprevalence data among current IDUs in Scotland[50,100]. Thirdly, 1,400 current IDUs were infected with HIV in Scotland during 1983-2000 (the majority during 1983-85 as described in 6.3.3.2.2). Fourthly, 1,500 former IDUs with chronic HCV infection and moderate disease in Scotland were assumed to have been initiated on antiviral therapy by the end of 2003 (as described in 6.3.3.4.3). All other parameters on cessation of injecting, characteristics of IDUs, HCV disease progression and mortality rates were retained the same as in Glasgow. The model for Scotland was fitted to record-linkage data on the estimated incident number of

decompensated cirrhosis cases for 1997-2001 (as described in 6.3.4; however, the period here was restricted to 1997-2001 because of the steeper rise in cases between 1996 and 1997 in Scotland (42%) than in Glasgow (30%), which may have resulted from later implementation of widespread HCV antibody testing across all regions).

6.4 Results

6.4.1 Assessment of HCV disease progression model

Models which excluded and included the relative risk effect of covariates (i.e. gender, age, co-infection with HIV and heavy alcohol use) on progression to cirrhosis and a range of uptake rates for heavy alcohol use (i.e. 0%, 20% and 40%) were assessed. Excluding the effect of covariates on progression to cirrhosis under-estimated the incident number of decompensated cirrhosis cases among ever IDUs in Glasgow between 1996-2001 (a mean total of 72 was modelled compared to 158 estimated through record-linkage, Table 4.6); and in only 9% of simulations was consistency achieved with record-linkage results. Model consistency improved to 15%, 27% and 40% following the inclusion of the covariate effects with rates of heavy alcohol use at 0%, 20% and 40%, respectively. Covariate-specific relative risk estimates for progression to cirrhosis among HCV chronically infected individuals produced by consistent simulations were similar to those employed a priori: 1.57 (95% CI 1.20-2.06) for males, 1.08 per year (1.04-1.12) for age at HCV acquisition, 2.82 (1.74-4.97) for HIV co-infection, and 2.38 (1.72-3.43) for heavy alcohol use.

Simulations which achieved consistent results had employed a higher progression to cirrhosis at 20 years than had been assumed initially based on published studies (i.e. 6.5%, 95% CI 3.5-9.5%). Therefore, increasing the overall progression to cirrhosis at 20 years to 7.5% (95% CI 5-10%) generated higher

consistency still: 53% in the Glasgow model with covariate effects and 40% uptake of heavy alcohol use, and 27% with the equivalent model for Scotland. The consistent simulations from these models were used to generate outcomes hereafter. Applying a different model fitting approach, which compared simulated results with 50 realisations from the Poisson distribution using a χ^2 goodness-of-fit measure with a 95% critical value, produced a slightly higher consistency for the Glasgow model of 59%.

6.4.2 Comparison of modelled and available epidemiological data

6.4.2.1 The prevalent number of current IDUs

The modelled prevalent numbers of current IDUs in Glasgow (mean and 95% CI for years 1990 and 2000: 8,400, 7,500-9,700; and 7,000, 6,200-8,400, respectively) and Scotland (mean and 95% CI for years 1990 and 2000: 22,200, 18,700-26,700; and 26,000, 19,000-37,200, respectively) were consistent with published estimates generated mainly through capture-recapture studies (Glasgow 1990 and 2000: 8494, 95% CI 7,490-9,720[18]; 7187, 95% CI 6,085-8,615[100], respectively; and Scotland 1990 and 2000: 21,700[108] and 25,140[100,152], respectively).

Of the modelled mean of 7,000 current IDUs in Glasgow during 2000, 28%, 59% and 13% were estimated to be aged <25, 25-34 and ≥35 years, respectively; a distribution which was slightly younger than that derived through capture-recapture techniques (23%, 63% and 14%, respectively; personal communication: Dr. Gordon Hay, University of Glasgow). For all Scotland, 31%, 58% and 11% were estimated to be aged <25, 25-34 and ≥35 years, respectively; a distribution which was comparable with that derived through capture-recapture techniques (30%, 56% and 14%, respectively; personal communication: Dr. Gordon Hay, University of Glasgow).

6.4.2.2 The annual number of drug-related deaths

The modelled mean annual number of deaths among current IDUs, unrelated to HCV and HIV, was in the range 100-110 (limits of 95% CIs: 70-160) and 350-390 (220-640) between 1999-2002 for Glasgow and Scotland, respectively. Given that 90% of these deaths were drug-related[305], these ranges compare reasonably with the reported number of drug-related deaths during this period by the Scottish General Register Office of 96-126 for Glasgow and 291-382 for Scotland[306].

6.4.2.3 The prevalence of HCV infection among current IDUs

The modelled seroprevalences of HCV among current IDUs in Glasgow (mean and 95% CI for years 1990 and 2000: 71%, 62-81%; and 62%, 53-73%, respectively) and Scotland (mean and 95% CI for years 1990 and 2000: 58%, 46-67%; and 45%, 38-52%, respectively) were generated in accordance with published epidemiological data (Glasgow 1990-91 and 2000: 74%, 95% CI 67-82%[47]; 62%, 95% CI 58-66%[50], respectively; and Scotland 2000: 44%, 95% CI 30-54%[100]).

6.4.2.4 The incident number of HCV-related decompensated cirrhosis cases

Figure 6.2 presents the modelled and expected annual incident number of decompensated cirrhosis cases among HCV chronically infected IDUs in (a) Glasgow and (b) Scotland during 1980-2030. The number of IDUs with newly developed decompensated cirrhosis each year was estimated to double approximately between 2000 and 2020 in Glasgow (26 to 61; 95% CIs 16-38 and 33-99, respectively) and Scotland (81 to 154; 95% CIs 61-101 and 90-236, respectively). During periods 1990-1995 and 1996-2001, 15-23% and 7-12% of HCV-related decompensated cases in

Scotland, respectively, were estimated to be co-infected with HIV (compared to 5-10% and 2-4% in Glasgow, respectively), which contributed to the sharp rise in cases during the earlier period.

6.4.3 Modelled HCV disease burden among IDUs in Glasgow and Scotland

Figure 6.3 illustrates the rise in the prevalent number of HCV infected (both current and former) IDUs in (a) Glasgow and (b) Scotland from only 1,700 (95% CI 800-2,800) and 3,800 (1,900-6,100) in 1980 to 15,700 (12,700-20,600) and 37,800 (28,000-53,200) in 2000, respectively. The prevalent number continued to increase during 2001-30 as a result of applying the estimated incidence of HCV infection from 2000 in subsequent years. In 2000, 12,100 (9,700-15,800) and 28,700 (21,200-40,700) in Glasgow and Scotland, respectively, were estimated to have chronic HCV infection; 8,700 (6,300-12,600) and 19,900 (13,700-29,200) of these, respectively, were among former IDUs (Table 6.4). Among HCV chronically infected former IDUs in Glasgow, the number with moderate disease was estimated to increase 2.5, 3.7 and 4.1 -fold between 2000 (a mean of 2,100; 95% CI 1,200-3,700) and 2010 (5,200; 3,600-7,400), 2020 (7,800; 5,800-10,300) and 2030 (8,600; 5,600-12,300), respectively. The prevalent number of cirrhotic HCV infected (both current and former) IDUs in Glasgow were estimated to rise 1.6, 2.4 and 2.6 -fold between 2000 (mean of 500; 95% CI 400-700) and 2010 (800; 600-1,200), 2020 (1,200; 700-1,800) and 2030 (1,300; 700-2,400), respectively.

6.4.4 Modelled stage of HCV disease by age among Glasgow IDUs in 2005

Figure 6.4 illustrates the estimated increasing severity of HCV disease with age among current and former Glasgow IDUs in 2005. The mean prevalence of moderate

disease and cirrhosis increased from 2% and 0% among (both current and former) IDUs aged under 30 years to 32% and 17% among those aged 50 years or more, respectively. Of relevance in terms of targeting HCV treatment, the mean estimated prevalence of moderate disease in 2005 was 16% and 27% among all former IDUs aged 30-39 and 40-49 years, respectively.

6.4.5 Modelled HCV disease progression over 45 years among Glasgow IDUs who commenced injecting in 1985

Figure 6.5 illustrates the mean progression of a cohort of Glasgow IDUs through 45 years following their commencement of injecting in 1985 (at mean age of 17.5 years). The mean percentage of IDUs who had died from HCV-related causes (i.e. liver failure and HCC) was 11% within 45 years of their injecting debut, and a further 11% and 40% had died from causes unrelated to HCV (or HIV) as current and former IDUs, respectively.

6.4.6 Modelled impact of different treatment scenarios on severe HCV disease

A total of 2,180 IDUs in Glasgow were estimated to develop severe HCV disease (consisting of 1,460 and 720 cases of decompensated cirrhosis and HCC, respectively) during 2005-2030, with no uptake of antiviral therapy. Table 6.4 (a) shows the number of cases of severe HCV-related disease that could be prevented during 2005-30 among IDUs in Glasgow through a range of antiviral treatment strategies. An estimated 60 cases, and only 3% of the total number, of severe disease could be prevented over 2005-30 with the current level of treatment to former IDUs (with moderate HCV disease) in Glasgow of 75 treated cases per year. Increasing the number initiated on antiviral therapy from 75 to 250, 500 and 1,000 former IDUs

(with moderate disease) per year was estimated to prevent a further 100, 230 and 350 severe HCV disease cases, respectively. Almost twice as many severe HCV events could be prevented if former IDUs with compensated cirrhosis had the same opportunity to be initiated on, and if they could respond as well to, antiviral therapy as those with moderate disease.

Of the 2,180 IDUs in Glasgow who were estimated to develop severe HCV disease during 2005-2030, 1,690 (78%) had become cirrhotic post 2005. Tables 6.4 (b) and (c) show the number of severe HCV-related disease events during 2005-30, among the 1,690 who had become cirrhotic post 2005, which could potentially be prevented and not prevented (i.e. unsuccessfully treated), respectively, by a range of antiviral treatment strategies. Only 3% to 27% of severe HCV-related events during 2005-30, among those who became cirrhotic post 2005, could be prevented by treatment of 75 to 1,000 former IDUs, respectively, with either mild or moderate HCV disease; however, a further 6% to 43% had been treated unsuccessfully, respectively. Thus, treatment with more effective antiviral therapies, than currently available, of 75 to 1,000 former IDUs (with either mild or moderate HCV disease) could potentially prevent in the ranges 3-9% and 27-70% of severe HCV-related events during 2005-30, respectively. Similarly, treatment of 75 to 1,000 former IDUs – with either moderate disease or compensated cirrhosis – could potentially prevent in the ranges 4-15% and 28-96% of severe HCV-related events during 2005-30, respectively (Table 6.4).

6.5 Discussion

This is the first attempt to estimate the current and future burden of HCV disease in Scotland related to injecting drug use, which will aid the planning of a public health

response to this epidemic. A total of 17,400 (95% CI 14,300-22,200) and 42,900 (32,400-60,600) persons, who had ever injected drugs, were estimated to be living with HCV antibodies by the end of 2003 in Glasgow and Scotland, respectively. This compares with approximately 5,000 (29%) and 13,900 (32%) diagnosed, respectively (assuming 77% of all diagnosed cases were IDUs and alive at the end of 2003, Chapter 4). Of these HCV-infected IDUs in Glasgow and Scotland, 13,200 (95% CI 10,800-16,900) and 32,200 (24,300-45,500) were estimated to be living with chronic HCV and therefore at risk of developing cirrhosis. In Glasgow and Scotland respectively, it was further estimated that 210 (95% CI 140-330) and 750 (490-1,060) HCV-infected IDUs had died prematurely from liver failure by the end of 2003, mainly over the last decade; this compares with 38 and 352 IDUs known to have died from AIDS in Glasgow and Scotland, respectively (Personal Communication: Glenn Codere, SCIEH).

The number of IDUs developing HCV-related decompensated cirrhosis in Scotland is estimated approximately to double between 2000 and 2020. Modelling efforts in other countries have predicted similar rises in HCV-related complications: mortality from HCV-related liver disease is estimated to increase 2-fold between 2000 and 2020 in the United States[82,84], 2.5-fold between 1990 and 2020 in France[79], and 1.9-fold between 1998 and 2020 in Switzerland[86]; in Australia, the number of people living with HCV-related cirrhosis is estimated to more than triple between 2000 and 2020[81].

Several countries have developed models to forecast the future course of their HCV epidemic, but few have validated their predictions, as in this study, by fitting model outcomes to past epidemiological trends relating to HCV and its consequences[79,83]. The aim here was to capture the essential features of the HCV

epidemic among IDUs, initially in Glasgow because more epidemiological data exist for this region than elsewhere in Scotland, and calibrate model parameters with data, principally, on the prevalent number of current IDUs, the prevalence of HCV infection among current IDUs and the incident number of HCV-related decompensated cirrhosis cases among IDUs. Insights gained from the model fitting process in Glasgow, such as on the rate of progression to cirrhosis, were used to apply the model to the whole of Scotland.

The importance of including the effect of age and gender on the progression of chronic HCV in models has previously been illustrated[79,83], but the potential limitation, in terms of under-estimating HCV disease burden, of excluding the influence of alcohol abuse and HIV co-infection has mostly only been acknowledged[79,82,86]. Discounting the influence of these four factors on disease progression and assuming a prevalence of cirrhosis at 20 years of 6.5% (95% CI 3.5-9.5%), consistent with a recent systematic review[94], under-estimated the number of IDUs developing liver failure in Glasgow during 1996-2001 by more than half that expected from the record-linkage data (Chapter 4). For Glasgow, consistency between model and record-linkage data improved by allowing disease progression rates to depend on age at HCV acquisition, gender, HIV co-infection and heavy alcohol use. However, the results still indicated that either (i) the prevalence of cirrhosis at 20 years was higher than the mean of 6.5% assumed, (ii) the increased rate of disease progression by co-factors – age, gender, HIV co-infection and alcohol – had been under-estimated, or (iii) the heterogeneity in progression had not been fully explained.

Projections clearly rely on the accuracy of the model assumptions used to derive them. The expected numbers of IDUs developing decompensated cirrhosis, data which are integral to the model fitting process, were based on the number of

HCV diagnosed individuals admitted to hospital with this complication, which were then adjusted to account for the proportion associated with injecting drug use (88%) and the non-hospitalisation (14%) and non-HCV-diagnosis (18%) of decompensated cases (Chapter 4). To allow for the uncertainty in the estimated number of IDUs developing decompensated cases, the 99.9% critical value with the χ^2 test statistic was used to assess the goodness-of-fit. The specification of ranges around model parameters were derived, through the synthesis of numerous sources of data from various studies, to encompass the full span of plausible values, but more formal methods for developing prior distributions for each parameter might allow a full Bayesian approach to model fitting.

As new data become available, improvements in the modelling of the HCV epidemic in Scotland, as elsewhere, will be possible, leading to further refinement in these estimates. In particular, further research is needed to validate estimates of the incidence and cessation of injecting drug use, to examine the prevalence of heavy alcohol use by gender among current and former IDUs, and to assess the influence of age and gender on injector mortality[152]. Although mortality related to heavy alcohol use[307] was not dealt with separately, the model assumed a raised risk of death from causes unrelated to HCV or HIV (i.e. two to five times higher the average age and gender general population specific rates)[73,292]. The annual incidence of HCV infection estimated in 2000 was carried forward to years 2001-30, but clearly could be influenced by the impact of future prevention initiatives and therefore the numbers progressing to moderate, but unlikely severe, disease could be over-estimated.

It was important to model the progression to moderate disease (defined as 3-5/6 on fibrosis and/or >3/18 on necroinflammation grades), even with the limited data available, because patients reaching this stage are recommended for treatment with

antiviral therapy[289]. Progression to moderate disease was based on the prevalence of necroinflammation activity, which can fluctuate over time[308], either because it is not continuously present or identifiable[309], but was regarded as cumulative for the purposes of modelling. A comprehensive review of the literature on progression following development of compensated cirrhosis revealed higher annual rates to decompensated cirrhosis (6.5%) and HCC (3.5%) than had been used in previous model applications (4% and 0.5-2%, respectively)[68,73,77,78,80,82].

Compared to the number of people living with chronic HCV infection in Scotland, relatively few have received antiviral therapy. Progress needs to be made in (i) identifying individuals who would most benefit from antiviral therapy and (ii) retention of those diagnosed with chronic HCV in clinical follow-up. A total of 3,000 (95% CI 1,800-4,800) and 6,600 (3,900-10,300) former IDUs were estimated to be living with moderate HCV disease in 2003 in Glasgow and Scotland, respectively; if the uptake of antiviral therapy continues at the current level, these numbers were estimated to double by 2010. As high as 16% and 27% of Glasgow former IDUs in 2005 aged 30-39 and 40-49 years, respectively, were estimated to have moderate disease (32% and 47% of those chronically infected, respectively), which highlights the potential benefit of targeting HCV testing at these age groups of former IDUs.

Treatment of chronic HCV with combination therapy of pegylated interferon plus ribavirin has been shown to be cost-effective[73,310] and is expected to reduce future disease complications. In France, however, it has been demonstrated that at least half of their HCV-infected population would require antiviral therapy to curb the future rise in the number of HCV-related deaths and at most reduce the incidence of decompensated cirrhosis by almost a quarter over the next twenty years[79]. Increasing uptake of antiviral therapy among former IDUs in Glasgow by more than thirteen-

fold, to 1,000 cases per year during 2005-2030, similarly did not have a dramatic impact on the future incidence of severe HCV disease, with reductions of only 19 to 28% depending on whether patients with compensated cirrhosis could be treated and respond to therapy as well as those with moderate disease. However, the treatment, with more effective antiviral therapies than currently available, of up to 1,000 former IDUs per year in Glasgow with moderate HCV disease over the next 26 years (15,000 cases in total and 62% of those HCV infected by the year 2030) could potentially prevent between 24% and 86% of severe HCV-related events during 2005-2030.

The simulations did not consider the different response to antiviral therapy according to genotype, the re-treatment of non-responders or that patients who had not responded to antiviral therapy may have benefited from a reduced rate of liver disease progression[311,312]. Thus, the model may have under-estimated the potential long-term benefit of antiviral therapy, but illustrates that current practice, with treatment of a relative minority of HCV infected patients, will scarcely impact on the future burden of this disease.

There is some urgency for action because HCV is frequently asymptomatic until cirrhosis develops. Once hepatic decompensation occurs, treatment is limited by the shortage of donor transplant organs. Additional research regarding the cost-effectiveness of HCV testing strategies targeted at former IDUs should be pursued to help formulate public health policy in this area. The identification and treatment of a larger proportion of former IDUs with advanced HCV disease, education about the importance of minimal alcohol consumption, and the development of better tolerated therapies may help to achieve a greater impact on the morbidity and mortality of this disease. Meanwhile, the development of initiatives to prevent (i) the further spread of

HCV infection among current IDUs and (ii) the initiation of non-IDUs into injecting should not be neglected.

Figure 6.1: Schematic outline of modelled HCV disease states which current and former injecting drug users (IDUs) progress through in model according to defined transition rates described in methods and Table 6.2.

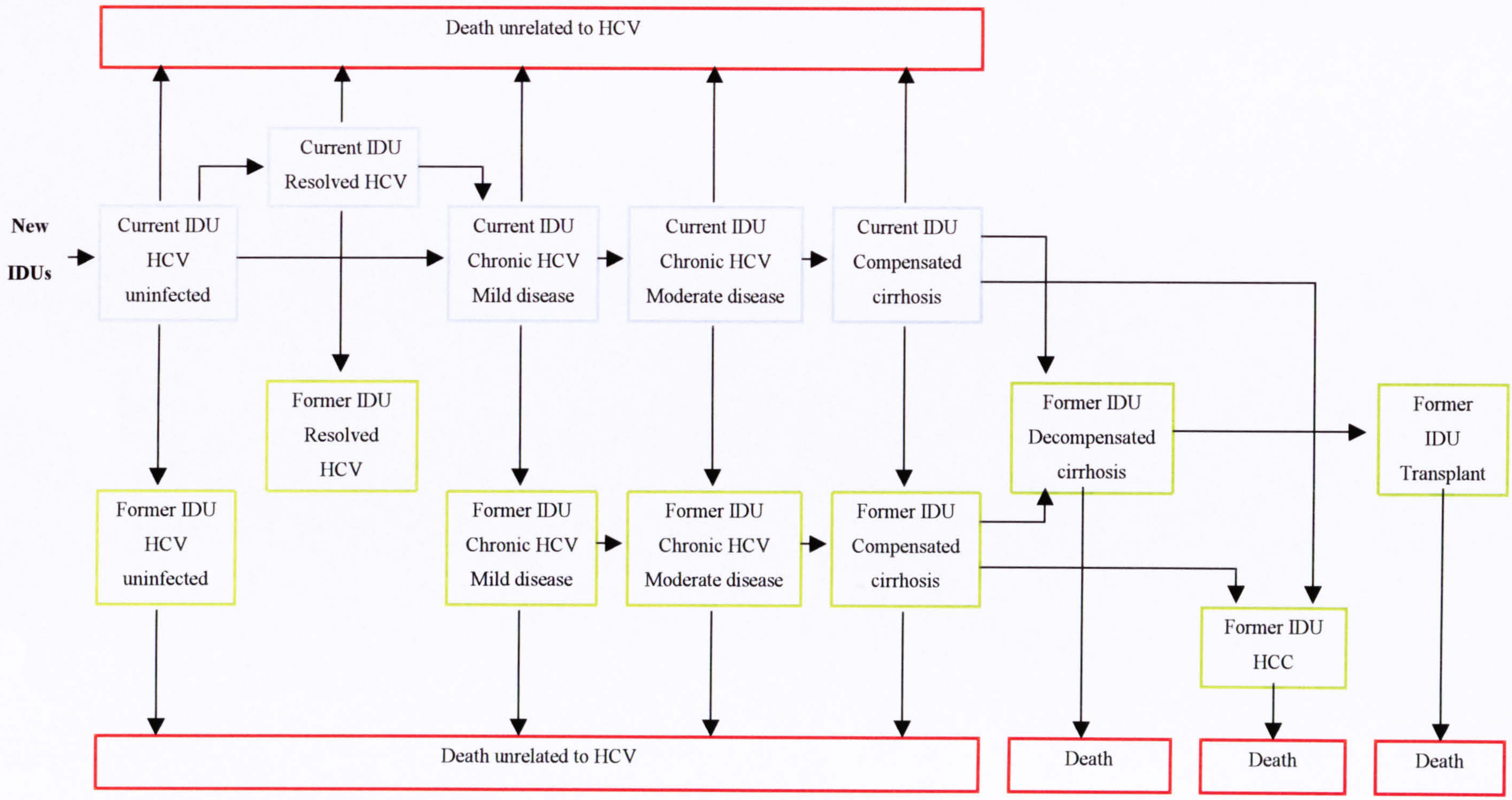


Table 6.1: Characteristics and progression from chronic HCV to moderate disease (defined as 3-5/6 on fibrosis and/or >3/18 on necro-inflammatory scores) among community-based studies.

Reference	**Country**	**Recruitment method**	**N**	**% IDU from known risk cases**	**Mean age at HCV acquisition (years)**	**% female**	**% HIV antibody positive**	**% heavy alcohol use (definition)**	**Median duration of HCV infection* (years)**	**Estimated cumulative percentage of chronic HCV at follow-up with:**		**Estimated prevalence (95% CI) of moderate to severe disease at 20 years¶**
										Inflammation grade 4-18	Fibrosis stage 3-6	
Kenny-Walsh, 1999[313]	Ireland	Retrospectively screened anti-D immune globulin recipients	376	0%	28.0	100%	-	5.0% (17/338) (≥14unit/wk)	17.0	54.8%	16.5%	64.5% (59.5-69.4%)
Wiese, 2000[314]	Germany	Retrospectively screened anti-D immune globulin recipients	500	0%	24.0	100%	0.0%	2.0% (>40g/day)	20.0	42.2%	4.0%	42.2% (37.8-46.7%)
Thomas, 2000[315] Rai, 2000[316]	USA	Community outreach[317]	997	100%	20.3	22%	33.4%	25.8% (≥260g/wk)	22.5	70.5%	15.0%	62.7% (59.6-65.7%)
Pooled estimate (random effects)												56% (43-70%)

* Mean stated if median not available. - Data missing.

¶ Estimated based on least squares linear regression. Moderate to severe disease prevalence was essentially based on prevalence of inflammation grade 4-18.

Table 6.2: Assumed risk of cirrhosis at twenty and thirty years* following infection with HCV according to risk profile of HCV chronically infected individuals.

Characteristics influencing HCV disease progression				**Prevalence of cirrhosis at: (mean and 95% CI)**	
Gender	**Age at HCV acquisition (years)**	**Co-infected with HIV**	**Heavy alcohol user**	**20 years**	**30 years**
Female	20	No	No	3.0% (2.4- 3.0%)	5.8% (4.4- 7.7%)
Female	20	No	Yes	6.6% (3.8- 9.1%)	12.8% (6.9-20.6%)
Female	20	Yes	No	8.4% (3.9-13.1%)	14.8% (7.1-27.9%)
Female	20	Yes	Yes	16.9% (6.2-33.5%)	28.7% (10.9-53.5%)
Female	30	No	No	6.2% (3.3- 8.6%)	12.2% (6.0-19.6%)
Female	30	No	Yes	13.9% (5.6-23.8%)	24.0% (9.9-43.6%)
Female	30	Yes	No	16.1% (5.6-31.5%)	29.0% (10.0-51.3%)
Female	30	Yes	Yes	31.6% (9.2-56.6%)	45.3% (15.9-63.8%)
Male	20	No	No	4.5% (2.9- 6.0%)	8.8% (5.2-14.2%)
Male	20	No	Yes	9.6% (4.6-17.1%)	17.5% (8.5-33.6%)
Male	20	Yes	No	11.8% (4.6-24.1%)	21.3% (8.6-43.4%)
Male	20	Yes	Yes	24.1% (7.7-47.4%)	38.9% (13.4-61.0%)
Male	30	No	No	9.0% (4.2-16.6%)	16.9% (7.6-33.6%)
Male	30	No	Yes	18.7% (6.7-38.1%)	31.8% (12.0-56.5%)
Male	30	Yes	No	22.8% (6.9-47.2%)	36.5% (12.2-60.5%)
Male	30	Yes	Yes	39.2% (11.3-62.2%)	52.7% (18.6-63.9%)

* Progression to compensated cirrhosis was calculated based on a Weibull distribution with prevalence estimated at 6.5% (95% CI 3.5-9.5%) and 20% (10-40%) after 20 and 40 years, respectively, and adjusted for increased progression with older age at HCV acquisition (relative risk 1.08 per year, 1.04-1.12), males (1.56, 95% CI 1.21-2.03), co-infection with HIV (2.92, 1.70-5.01), and heavy alcohol use (2.33, 1.67-3.26).

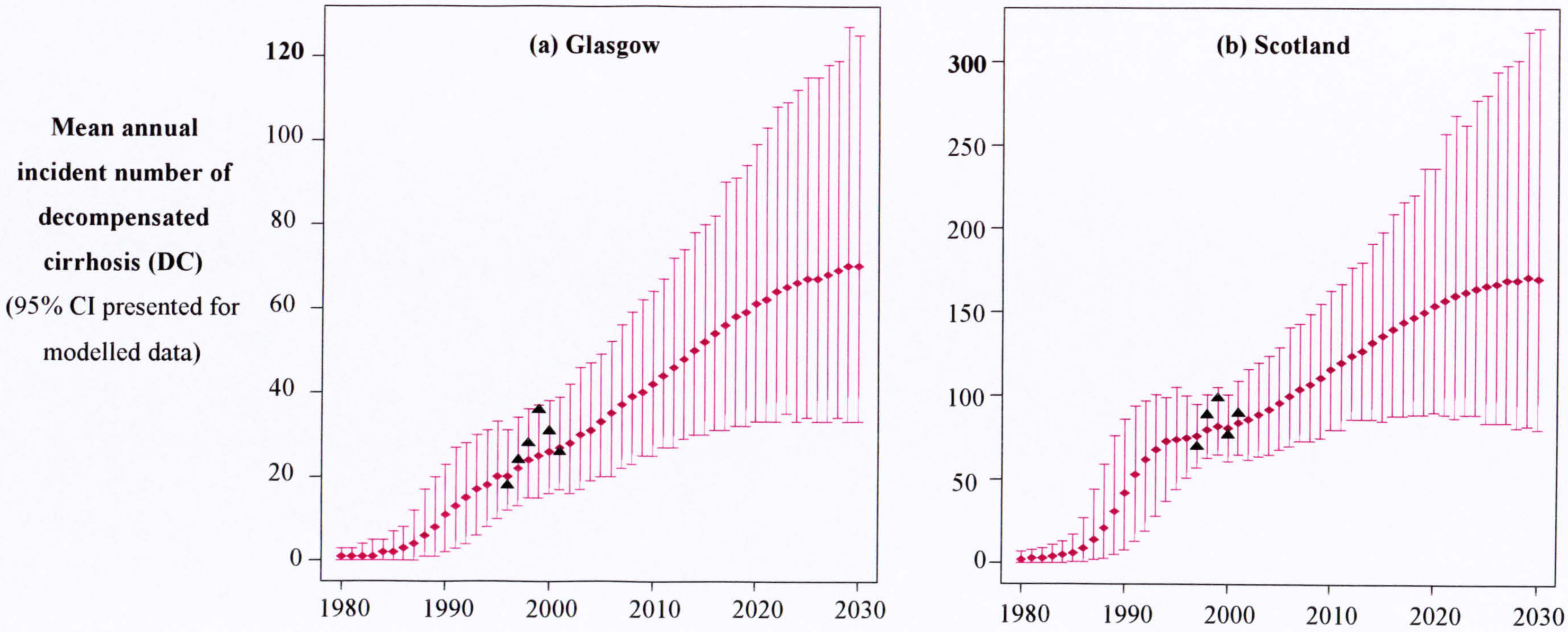
Table 6.3: Estimated annual transition probabilities for progression of HCV infected cirrhotic persons.

Progression between disease states		**Average annual transition rates estimated from literature**			**Pooled estimate (95% CI*)**
Initial state	Outcome	Point estimate	Total number of subjects (mean years of follow-up)	First author (reference no)	
(i) Compensated cirrhosis	Decompensated cirrhosis (¶ unrelated to HCC)	3.9%¶‡ 4.9%¶‡ 6.4%¶ 9.1%¶ 9.7%†	355 (5.1 years) 112 (4.5 years) 136 (6.6 years) 44 (3.3 years) 257 (5.3 years)	Fattovich et al. ([318]) Hu et al. ([319]) Fattovich et al. ([320]) Serfaty et al. ([321]) Gines et al. ([322])	6.5% (4.0-9.2%)
(ii) Compensated cirrhosis	HCC	0.7% 1.0%† 1.4%‡ 2.1%‡ 2.1% 2.5%‡ 2.8%‡ 3.4%† 4.6% 4.7% 5.1%† 5.1% 6.9% 12.3%†	124 (6.1 years) 405 (8.0 years) 384 (5.1 years) 112 (4.5 years) 136 (6.6 years) 163 (5.3 years) 416 (5.7 years) 396 (4.2 years) 166 (5.5 years) 349 (5.8 years) 228 (3.7 years) 44 (3.3 years) 45 (5.5 years) 400 (3.0 years)	Takano et al. ([323]) Gentilini et al. ([324]) Fattovich et al. ([318]) Hu et al. ([319]) Fattovich et al. ([320]) Bruno et al. ([325]) Degos et al. ([326]) Mandelli et al. ([327]) Chiaramonte et al. ([328]) Ikeda et al. ([329]) Imberti et al. ([330]) Serfaty et al. ([321]) Nishiguchi S at al. ([331]) Tsai et al. ([332])	3.5% (2.4-4.6%)
(iii) Decompensated cirrhosis	Liver transplant	2.1%	507 (1.9 years)	Hutchinson et al. (Ch. 4)	2.0%*
(iv) Decompensated cirrhosis	Death	12.6%‡ 12.9%‡ 14.0% 22.3% 30.7%†	24 (-) 65 (2.0 years) 49 (-) 507 (1.9 years) 121 (-)	Fattovich et al. ([320]) Fattovich et al. ([318]) Hu et al. ([319]) Hutchinson et al. (Ch. 4) Gines et al. ([322])	18.6% (13.7-25.0%)
(v) HCC	Death	54.0% 57.6%‡ 63.9%†	70 (0.7 years) 60 (-) 2573 (-)	Hutchinson et al. (Ch. 4) Degos et al. ([326]) El-Serag et al. ([333])	60.5% (54.5-67.6%)
(vi) Liver transplant (for decompensated cirrhosis)	Death in first year	5.2% 6.0% 7.0% 10.0% 13.0% 16.0% 20.0% 21.0% 21.8% 22.1%	58 (3.1 years) 97 (-) 54 (3.4 years) 128 (2.7 years) 209 (4.1 years) 510 (2.5 years) 3084 (-) 149 (3.0 years) 715 (9.4 years) 1080 (-)	Paik et al. ([334]) Ascher et al. ([335]) Shuhart et al. ([336]) Wali et al. ([337]) Neumann et al. ([338]) Ghobrial et al. ([339]) Detre et al. ([340]) Gane et al. ([341]) Jain et al. ([342]) Fagiuoli et al. ([343])	14.6% (11.1-18.2%)
(vii) Liver transplant (for decompensated cirrhosis)	Death in 2nd+ years	3.0% 3.1% 3.5% 3.6% 5.1% 5.1% 5.1% 6.5% 10.0%	149 (3.0 years) 1080 (-) 715 (9.4 years) 209 (4.1 years) 128 (2.7 years) 3084 (-) 510 (2.5 years) 54 (3.4 years) 58 (3.1 years)	Gane et al. ([341]) Fagiuoli et al. ([343]) Jain et al. ([342]) Neumann et al. ([338]) Wali et al. ([337]) Detre et al. ([340]) Ghobrial et al. ([339]) Shuhart et al. ([336]) Paik et al. ([334])	4.4% (3.5-5.3%)

† Includes HCV antibody negative persons; ‡ Includes persons who had received anti-viral therapy; (-) Data missing;

* Range/estimate used in model.

Figure 6.2: The expected (▲) and modelled (♦) annual incident number of decompensated cirrhosis cases among HCV chronically infected IDUs in (a) Glasgow and (b) Scotland, 1980-2030; models included the influence of increased progression among males, older age at HCV acquisition, co-infection with HIV and heavy alcohol use (40% uptake).



	(a) Glasgow					(b) Scotland				
Year	1990	2000	2010	2020	2030	1990	2000	2010	2020	2030
Mean annual incident number of DC (95% CI)	11 (2-23)	26 (16-38)	42 (25-64)	61 (33-99)	70 (33-125)	42 (8-86)	81 (61-101)	116 (80-163)	154 (90-236)	170 (80-320)

Figure 6.3: The modelled prevalent number of HCV infected IDUs in (a) Glasgow and (b) Scotland according to stage of HCV disease, 1960-2030.

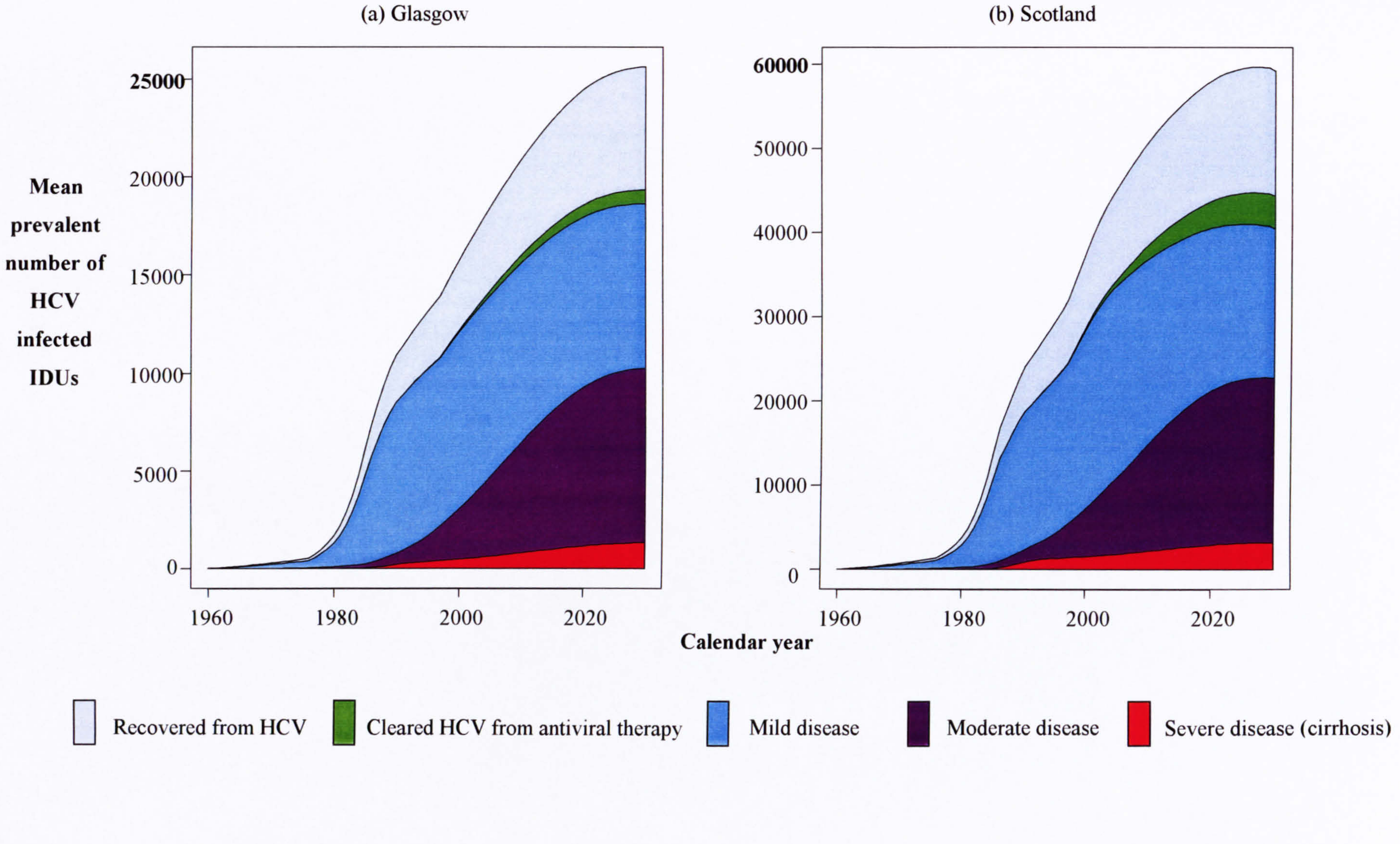
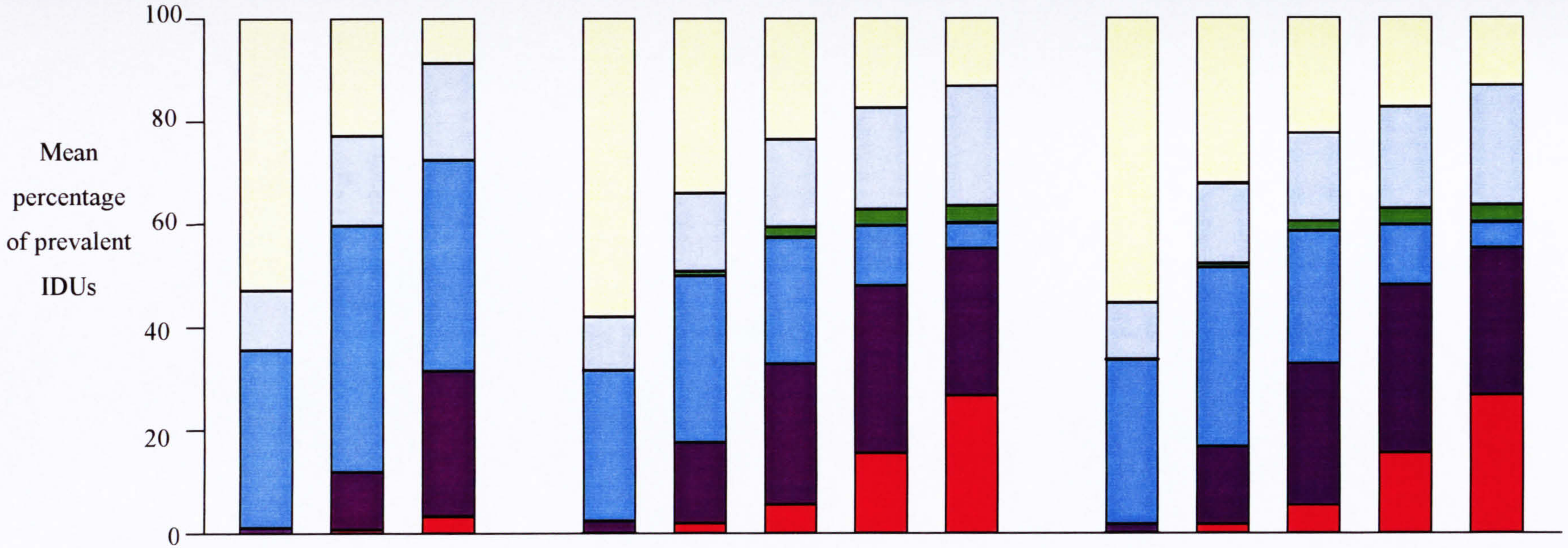


Table 6.4: The modelled prevalent number (mean and 95% CI) of IDUs in Glasgow and Scotland by stage of HCV disease and IDU status, 2000-2030.

Region	IDU status	HCV disease stage	Calendar year						
			2000	2005	2010	2015	2020	2025	2030
Glasgow	All	All IDUs	24260 (19060-32650)	29150 (22700-37850)	33680 (24890-43230)	37650 (26290-49040)	40880 (27170-54140)	43150 (27500-59060)	44440 (26940-63020)
		All HCV infected	15730 (12700-20580)	18450 (15050-23330)	20890 (16600-26200)	22930 (17270-28870)	24460 (17580-31930)	25340 (16990-34270)	25620 (16210-35840)
		All chronically infected	12090 (9710-15800)	13950 (11320-17770)	15610 (12150-19960)	16960 (12640-22010)	17950 (12590-24110)	18480 (12450-25840)	18620 (11890-27020)
		Mild	9040 (6300-12530)	9270 (6450-12550)	9160 (6080-12720)	8910 (5570-12990)	8670 (4920-13270)	8490 (4520-13330)	8380 (4310-13360)
		Moderate	2550 (1380- 4520)	4040 (2570- 6170)	5630 (3990- 7950)	7050 (5280- 9450)	8110 (6080-10830)	8700 (6280-12080)	8900 (5850-12950)
		Severe (cirrhosis)	500 (370- 660)	640 (470- 880)	820 (580- 1160)	1000 (660- 1480)	1170 (710- 1820)	1280 (710- 2160)	1340 (670- 2380)
	Former	All former IDUs	17280 (12100-25570)	22540 (16440-31000)	27210 (19460-36290)	31260 (21960-40890)	34540 (23250-46190)	36820 (23600-50600)	38100 (23150-54350)
		All HCV infected	11380 (8310-16390)	14460 (10990-19290)	17050 (12910-21890)	19180 (14500-24400)	20760 (15080-26530)	21640 (14960-28710)	21910 (14220-30280)
		All chronically infected	8730 (6260-12570)	10900 (8320-14620)	12670 (9630-16280)	14100 (10550-18250)	15120 (10780-20160)	15660 (10650-21520)	15790 (10110-22550)
		Mild	6150 (3800- 9570)	6660 (4280- 9700)	6640 (4180- 9350)	6430 (3800- 9360)	6200 (3420- 9560)	6030 (3150- 9540)	5910 (2910- 9600)
		Moderate	2130 (1170- 3690)	3630 (2300- 5490)	5230 (3650- 7370)	6680 (4900- 8980)	7760 (5790-10340)	8360 (6010-11360)	8550 (5630-12320)
		Severe (cirrhosis)	450 (320- 610)	610 (440- 840)	800 (560- 1140)	990 (640- 1460)	1150 (700- 1810)	1270 (710- 2140)	1320 (660- 2350)
Scotland	All	All IDUs	77480 (54990-118260)	89860 (65910-130160)	101830 (73330-140080)	112310 (79290-154850)	120700 (81510-167490)	126250 (82660-175230)	126680 (79600-178780)
		All infected	37840 (27960- 53160)	45480 (34840- 63210)	50890 (38230- 69000)	55110 (40610- 74250)	58100 (41010- 77340)	59500 (40510- 80240)	59150 (38710- 82680)
		All chronically infected	28700 (21250- 40720)	33830 (25620- 47340)	36890 (27060- 50840)	39100 (27260- 54080)	40510 (26930- 57830)	40970 (26180- 59680)	40400 (23980- 60720)
		Mild	21500 (13510- 31560)	22900 (14850- 34050)	22020 (13670- 32140)	20550 (12150- 30390)	19270 (10840- 29550)	18380 (9910- 29300)	17660 (9170- 28660)
		Moderate	5640 (3120- 9660)	9070 (5700- 14350)	12640 (7880- 19320)	15920 (9530- 24580)	18270 (10650- 27670)	19390 (10370- 29240)	19480 (9610- 29820)
		Severe (cirrhosis)	1560 (1300- 1920)	1860 (1450- 2490)	2240 (1650- 3090)	2630 (1740- 3660)	2970 (1760- 4610)	3190 (1710- 5610)	3260 (1600- 5940)
	Former	All former IDUs	51460 (34010- 81530)	69300 (49030-105230)	83290 (59760-121070)	94680 (66130-134150)	103520 (70610-145330)	109220 (71970-154450)	111430 (69550-158920)
		All infected	26310 (18190- 38640)	34850 (25400- 50440)	41500 (30840- 57980)	46470 (34520- 63340)	49850 (36110- 67060)	51410 (36000- 69030)	51320 (34550- 70930)
		All chronically infected	19920 (13680- 29220)	25740 (18600- 37490)	29740 (21360- 42240)	32530 (22510- 45940)	34240 (22470- 49380)	34820 (21530- 51600)	34450 (20150- 51770)
		Mild	13860 (8130- 21750)	16000 (9700- 24680)	16040 (9760- 24220)	15050 (8920- 22550)	13940 (7900- 21590)	13110 (6920- 21260)	12560 (6380- 20910)
		Moderate	4640 (2520- 7810)	7980 (4990- 12540)	11530 (7010- 17620)	14910 (8860- 23280)	17370 (9970- 26960)	18550 (9830- 28510)	18660 (9090- 29170)
		Severe (cirrhosis)	1420 (1140- 1780)	1760 (1360- 2330)	2160 (1600- 2950)	2570 (1690- 3610)	2930 (1740- 4560)	3160 (1680- 5530)	3230 (1580- 5800)

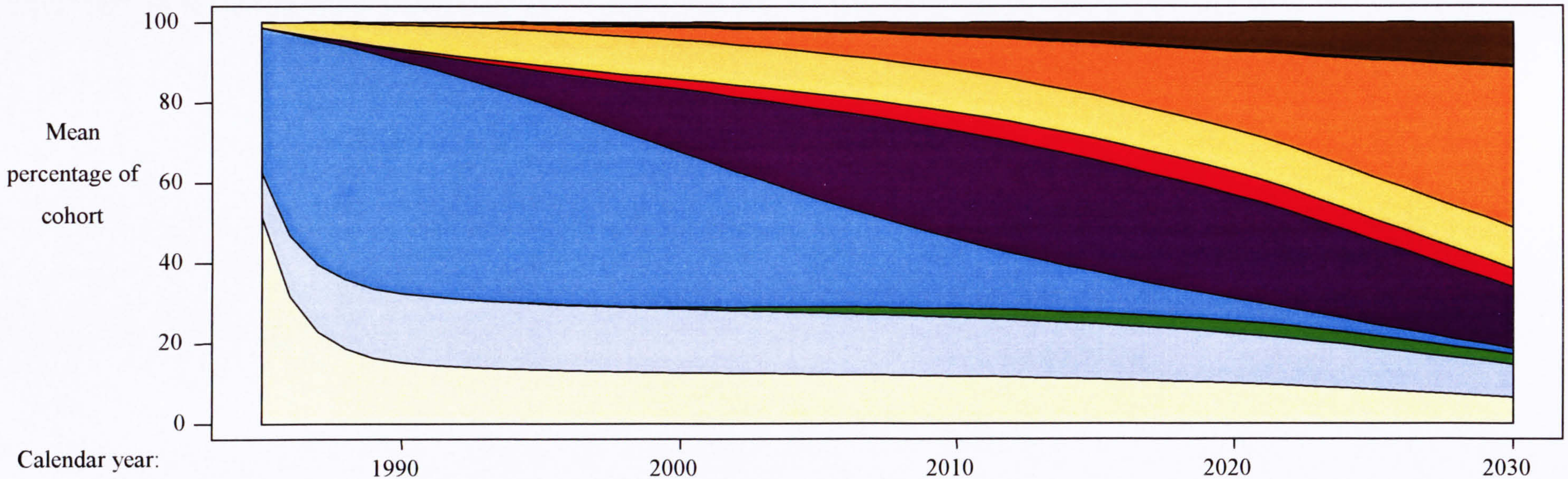
Figure 6.4: The modelled prevalent number of IDUs in Glasgow in 2005 according to stage of HCV disease, current age and IDU status.



Age (years): [Mean number]	<30 [3870]	30-39 [2350]	40-49 [390]	<30 [4080]	30-39 [12970]	40-49 [5150]	50-59 [280]	60+ [60]	<30 [7950]	30-39 [15320]	40-49 [5540]	50-59 [280]	60+ [60]
	Current IDUs			Former IDUs					All IDUs				
IDU status:													
HCV uninfected	53%	23%	9%	58%	34%	24%	18%	13%	56%	32%	23%	18%	13%
Recovered from HCV	11%	17%	19%	10%	15%	17%	20%	23%	11%	16%	17%	20%	23%
Cleared HCV*	0%	0%	0%	0%	1%	2%	3%	3%	0%	1%	2%	3%	3%
Mild disease	34%	48%	41%	29%	32%	24%	12%	5%	32%	35%	26%	12%	5%
Moderate disease	1%	11%	28%	2%	16%	27%	32%	28%	2%	15%	27%	32%	28%
Cirrhosis	0%	1%	3%	0%	2%	6%	15%	27%	0%	2%	5%	15%	27%

* From anti-viral therapy

Figure 6.5: The modelled progression of a mean of 1,800 IDUs in Glasgow who had commenced injecting in 1985 according to stage of HCV disease and deceased status.



HCV-related death	0%		1%		3%		7%		11%
HIV-related death	0%		0%		0%		0%		0%
Former IDU death	1%		3%		8%		20%		40%
Current IDU death	6%		10%		11%		11%		11%
Cirrhosis	0%		2%		5%		6%		4%
Moderate disease	2%		16%		27%		26%		15%
Mild disease	58%		39%		18%		6%		2%
Cleared HCV*	0%		0%		2%		3%		2%
Recovered from HCV	17%		16%		15%		12%		8%
HCV uninfected	15%		13%		12%		10%		6%

* From anti-viral therapy ** Unrelated to HCV or HIV

Table 6.5: The modelled number of severe HCV-related events (i.e. decompensated cirrhosis and HCC) potentially prevented and not prevented by antiviral therapy among IDUs in Glasgow during 2005-30 based on different (i) stages of HCV disease at which former IDUs were initiated on treatment and (ii) uptake rates of antiviral therapy.

(i) Stage of HCV disease at which former IDUs were initiated on treatment	**(ii) Maximum number initiated on therapy per year (mean number over the 26 years)**	**Severe HCV-related events during 2005-30 (Mean total = 2,180)**		**Severe HCV-related events during 2005-30, among those who became cirrhotic post 2005 (Mean total = 1,690)**			
		(a) Prevented by antiviral therapy (i.e. Successfully treated)		**(b) Prevented by antiviral therapy (i.e. Successfully treated)**		**(c) Not prevented by antiviral therapy (i.e. Unsuccessfully treated)**	
		Mean number prevented	Mean % of total events which were prevented	Mean number prevented	Mean % of total events which were prevented	Mean number of non-responders	Mean % of total events which were non-responders
Mild & Moderate disease	75 (1,950)	47	2%	47	3%	104	6%
	250 (6,500)	163	8%	153	9%	234	14%
	500 (12,993)	228	11%	227	13%	432	26%
	1000 (21,058)	456	21%	452	27%	725	43%
Moderate disease	75 (1,950)	57	3%	53	3%	165	10%
	250 (6,500)	157	7%	152	9%	403	24%
	500 (12,754)	283	13%	277	16%	764	45%
	1000 (15,328)	409	19%	402	24%	1042	62%
Moderate disease & compensated cirrhosis	75 (1,950)	92	4%	64	4%	185	11%
	250 (6,500)	310	14%	245	15%	478	28%
	500 (12,889)	510	23%	409	24%	878	52%
	1000 (16,116)	614	28%	471	28%	1150	68%

Chapter 7: Summary and future work

7.1 Overview of the approach used to derive HCV projections

A forward projection approach was used to model the number of, both current and former, IDUs who have acquired HCV infection and will either have progressed or will progress to mild, moderate and severe HCV disease. The HCV epidemic among IDUs in Glasgow was modelled initially because more epidemiological data exist for this region than elsewhere in Scotland, and model outcomes calibrated with local data relating to HCV and its consequences. Insights gained from the model fitting process in Glasgow were then used to extend the model to the rest of Scotland.

The HCV projection model incorporated both knowledge and uncertainty about major parameters relating to (i) the incidence and cessation of injecting drug use and mortality from causes unrelated to HCV, (ii) the incidence of HCV infection among current IDUs, and (iii) the rate of HCV disease progression. First, incidence and cessation of injecting drug use in Glasgow were derived through the use of a modified Delphi approach which combined expert opinion with capture-recapture IDU prevalence estimates. Mortality from causes unrelated to HCV among current and former IDUs was based on estimates from the literature. Secondly, stochastic simulation was developed to model the transmission of HCV among current IDUs in Glasgow, according to their injecting risk behaviours and the characteristics of the virus, and to estimate the past incidence of HCV infection. For the third component of the projection model, the worldwide literature was reviewed to inform the rate of HCV disease progression and a meta-analysis was performed to quantify the effect of heavy alcohol use on progression to cirrhosis in persons with chronic HCV. Finally, modelled outcomes were fitted to epidemiological data, in particular the number of

IDUs developing HCV-related decompensated cirrhosis each year which had been estimated through the record-linkage of Scotland's database of HCV diagnosed persons with hospital discharge and death records.

7.2 Main findings from stages undertaken to derive HCV projections

The following five sections provide a synopsis of the stages, and the main findings presented in Chapters 2-6, undertaken to derive projections: (i) estimating the incidence and cessation of injecting drug use in Glasgow, (ii) estimating the past incidence of HCV infection among injecting drug users in Glasgow, (iii) estimating the severe disease burden associated with HCV infection in Scotland, (iv) estimating the influence of alcohol on the progression of HCV infection, and (v) estimating the current and future disease burden of HCV among injecting drug users in Glasgow and Scotland.

7.2.1 Estimating the incidence and cessation of injecting drug use in Glasgow

Glasgow has been at the forefront of injecting drug use prevalence estimation: log-linear modelling of capture-recapture data estimated 8,490 (95% CI 7,490-9,720) and 7,190 (6,090-8,620) current IDUs in 1990 and 2000, respectively. Hitherto, however, no consensus had been sought on the size and shape of its IDU epidemic curve. A modified Delphi approach was used to elicit one for Glasgow. Twelve experts were asked to provide their opinion on the prevalent number, incident number, and percentage ceasing injecting each year for quinquennia during 1960-2000. Instead of the usual iterative process to refine experts' consensus, the elicitation of IDU incidence and cessation provided an opportunity, not previously explored, to combine

these data and examine coherence with capture-recapture estimates on the prevalent number of injectors during 1990 and 2000.

Scrutiny of consensus data indicated that experts had under-estimated incidence during 1985-1990, and over-estimated prevalence during 1995-2000 and cessation during 1985-2000. Coherent estimates indicated that prevalence (median estimates: 149 to 557), incidence (28 to 49) and cessation (1 to 2%) remained low and stable during 1960-1975, rose steeply between 1975-1985 (median prevalence from 557 to 4,438; incidence from 49 to 1,335; cessation from 2% to 6%), and by 2000 there had been a decline in incidence (1,195) but further rises in prevalence (6,809) and cessation (15%). Point prevalence estimates from capture-recapture studies were essential to anchor experts' consensus and derive coherent data. The rise in the cessation of IDU throughout the 1990s is a promising finding in the context of the expansion of methadone prescribing and other harm reduction services in Glasgow.

7.2.2 Estimating the past incidence of HCV infection among injecting drug users in Glasgow

Stochastic simulation was used to model quantitatively the transmission of HCV through the sharing of used needles/syringes among current IDUs in Glasgow during 1960-2000. The modelling combined information on (a) the incidence and cessation of injecting drug use in Glasgow, (b) the frequencies with which Glasgow IDUs injected and shared needles/syringes, and the numbers of different persons they shared with, and (c) the susceptibility, transmissibility and carriage of HCV infection.

The model that considered higher infectivity during acute viraemia following infection produced seroprevalences (median: 62-72%) and incidences (18-30 per 100 susceptible injector-years) consistent with observed data during the 1990s, and

suggests that this phenomenon may be an important factor in the spread of HCV, as recognised with HIV. Discounting this effect would have under-estimated HCV prevalence which, alternatively, could have been explained by the model's omission of transmissions occurring through other routes such as indirect sharing of injecting equipment. The annual number of new HCV infections among current IDUs (who had no previous infection) in Glasgow was estimated to be low during 1960-1976 (median of 10-60), rise steeply during the early 1980s to peak in 1985 (1,120), stabilise during 1991-1997 (510-610) and rise again during 1998-2000 (710-780). Scenario analyses indicated that potentially as many as 4,500 HCV infections (10^{th} and 90^{th} percentiles: 2,400-7,700) had been prevented in Glasgow during 1988-2000, as a result of harm-reduction measures introduced during this period.

Scenario analyses also permitted the gauging of changes in risk behaviours required to effect appreciable reductions in the incidence of HCV infection. Incidence can be successfully reduced if IDUs who, unavoidably, share needles/syringes confine their borrowing to one person; with this strategy alone (i.e. reducing the mean number of partners to one from an estimated 3-6, 2, and 3 during years 1988-1990, 1991-1997 and 1998-2000, respectively), an estimated 5,300 HCV infections (10^{th} and 90^{th} percentiles: 4,100-6,700) could have been averted during 1988-2000. Alternatively, permitting only 11-20% of IDUs in Glasgow to share a needle/syringe at least once annually during 1988-2000 would have similarly averted an estimated 5,200 HCV infections (10^{th} and 90^{th} percentiles: 4,200-6,600). Such insights will inform those responsible for developing new ways to prevent HCV transmission among IDU populations. A serious commitment to implement, and evaluate the cost-effectiveness of, strategies, which could achieve appreciable reductions in risk behaviours among IDUs, is urgently needed to influence the future course of the HCV epidemic.

7.2.3 Estimating the severe disease burden associated with HCV infection in Scotland

To monitor the emergence of sequelae related to HCV infection requires national surveillance systems, currently lacking in the UK and elsewhere, which detect not only advanced liver disease but also the aetiological factors. The laboratory reporting of diagnostic positive tests for HCV antibodies in Scotland linked electronically to clinical data gathered from hospital and death records provided a unique national epidemiological dataset on diagnosed HCV infection to estimate the numbers developing HCV-related decompensated cirrhosis and HCC.

A substantial proportion of persons who test positive for HCV antibodies report no risk factors for infection: 32% (3,874/12,096) in Scotland. Of 12,096 diagnosed HCV antibody positive persons studied in Scotland, 61% reported injecting drug use with their HCV diagnosis and a further 27%, yielding a total of 88%, were established as IDUs through log-linear modelling of record-linkage data from four sources (i.e. HCV diagnoses, HIV test, hospital and death records).

Approximately 500 and 200 diagnosed HCV antibody positive persons in Scotland had developed and died of liver failure, respectively, by the end of 2001. Relatively low prevalences of HCV infection were estimated among individuals with HCC and decompensated cirrhosis presenting to hospital (13% and 6%, respectively) or having died (11% and 5%, respectively) in Scotland during 1996-2001; these estimated rates incorporated adjustments to account for (i) the inability to link a proportion of HCV diagnosed persons due to insufficient identifiers and (ii) the non-diagnosis of HCV infection among HCV infected HCC and decompensated cirrhosis cases. The hospital morbidity data alone, however, under-estimated the incidence of

severe HCV-disease since 25% and 14% of HCV diagnosed individuals who had died – according to death records held by General Registrar Office for Scotland – from HCC and decompensated cirrhosis, respectively, were not identified with these conditions in the hospital register. The number of persons with newly developed HCV-related decompensated cirrhosis in Scotland was estimated to have increased by 30% from 230 (95% CI 220-250) in 1996-1998 to 300 (280-320) cases in 1999-2001, highlighting HCV as a growing significant burden on healthcare resources in Scotland.

Alcohol was a prominent factor among HCV diagnosed persons who had died (78% of 134) or were hospitalised (72% of 442) with decompensated cirrhosis during 1996-2001 in Scotland. The younger age of decompensated patients presenting to hospital in Scotland during 1996-2001 with both HCV and alcohol (78% of 320 were aged <50 years) suggests that the combined effect of these two factors accelerates liver disease progression more than if only one (decompensated cirrhosis patients with only HCV: 48% of 122; and with only alcohol: 33% of 8,465) or neither of these factors (17% of 1,681) were present. In light of the potential synergistic effect between alcohol and HCV, limiting the alcohol consumption of chronically infected individuals is important to help prevent future HCV-related morbidity and mortality.

7.2.4 Estimating the influence of alcohol on the progression of HCV infection

The elucidation of the factors that influence progression to severe HCV disease is important at an individual level – so that appropriate counselling of those affected and help in making decisions regarding antiviral therapy can be given – and at a population level – so that covariate influences in projection models aimed at estimating the future burden of disease can be accommodated. A convincing, yet

inconsistent, pattern which demonstrates increased progression of HCV-related liver disease with heavy alcohol use has emerged. A meta-analysis which examined twenty articles, involving over 15,000 HCV chronically infected persons, published between 1995 and 2004 was therefore undertaken to explore the relationship between advanced liver disease – either advanced fibrosis, cirrhosis or decompensated cirrhosis – and the consumption of alcohol.

The pooled RR of cirrhosis, including decompensated cirrhosis, associated with heavy alcohol intake (defined in the range of at least 210 to 560g per week) was 2.33 (95% CI 1.67-3.26) by the random effects model. The risk of HCV-related disease associated with heavy alcohol intake increased with severity of the outcome: the lowest (1.63; 95% CI 1.22-2.17) and highest (3.54; 2.14-5.85) pooled RR estimates were obtained for advanced fibrosis and decompensated cirrhosis, respectively. Studies varied widely in their definition of significant alcohol intake, ranging between 210 and 560g per week, and so the true threshold above which alcohol accelerates HCV disease progression remains uncertain.

Studying the relationship between HCV and alcohol is problematic because of difficulties in obtaining an accurate history of alcohol intake. Moreover, studies investigating the risk of HCV-related cirrhosis necessarily include patients undergoing liver biopsy and therefore could under-represent heavy alcohol users, as patients consuming alcohol at toxic levels may have been precluded from biopsy. Such selectivity may have under-estimated the regression effect of alcohol in the meta-analysis. Nevertheless, the evidence overwhelmingly shows a worsened outcome for those with chronic HCV and concurrent alcohol use. Alcohol consumption should be minimised as much as possible in those who have chronic HCV until a safe threshold is more definitively determined.

7.2.5 Estimating the current and future disease burden of HCV among injecting drug users in Glasgow and Scotland

To plan a public health response to the HCV epidemic in Scotland, in terms of both treatment needs and preventive measures, quantitative estimates of the current and future burden of HCV disease are required. The aims were to develop a model to estimate (i) the numbers of, both current and former, IDUs who acquired HCV infection and progressed to mild, moderate and severe HCV disease in Glasgow and Scotland between 1960 and 2030, and (ii) the number of cases of severe HCV-related disease (i.e. decompensated cirrhosis and HCC) among IDUs that could be prevented in the future through a range of antiviral treatment strategies. Several countries have developed models to forecast the future course of their HCV epidemic, but few have validated their predictions, as in this study, by fitting model outcomes to past epidemiological trends relating to HCV and its consequences.

A total of 17,400 (95% CI 14,300-22,200) and 42,900 (32,400-60,600) persons, who had ever injected drugs, were estimated to be living with HCV antibodies by the end of 2003 in Glasgow and Scotland, respectively. This compares with approximately 5,000 (29%) and 13,900 (32%) diagnosed, respectively. Of these HCV-infected IDUs in Glasgow and Scotland, 13,200 (95% CI 10,800-16,900) and 32,200 (24,300-45,500) were estimated to be living with chronic HCV and therefore at risk of developing cirrhosis. The number of IDUs developing HCV-related decompensated cirrhosis in Scotland is estimated approximately to double between 2000 and 2020.

Consistency between model and record-linkage data improved by allowing disease progression rates to depend on age at HCV acquisition, gender, HIV co-

infection and heavy alcohol use. However, the results still indicated that either the prevalence of cirrhosis at 20 years was higher than the mean of 6.5% assumed or the strength of factors influencing progression had not been fully explained. A review of the literature on progression following development of compensated cirrhosis revealed higher annual rates to decompensated cirrhosis (6.5%) and HCC (3.5%) than had been used in previous model applications (4% and 0.5-2%, respectively).

A total of 3,000 (95% CI 1,800-4,800) and 6,600 (3,900-10,300) former IDUs were estimated to be living with moderate HCV disease in 2003 in Glasgow and Scotland, respectively; if the uptake of antiviral therapy continues at the current level, these numbers were estimated to double by 2010. As high as 16% and 27% of Glasgow former IDUs in 2005 aged 30-39 and 40-49 years, respectively, were estimated to have moderate disease (32% and 47% of those chronically infected, respectively), which highlights the potential benefit of targeting HCV testing at former IDUs who belong to these age groups.

The treatment with antiviral therapy of 15,000 former IDUs in Glasgow with moderate HCV disease over the next 26 years (62% of those HCV infected by the year 2030) could potentially prevent between 24% (based on 45% response and compliance to therapy) and 86% (based, unrealistically, on 100% response and compliance to therapy) of severe HCV-related events during 2005-2030. The identification and treatment of a larger proportion of former IDUs with HCV disease, education about the importance of minimal alcohol consumption, and the development of more effective and better tolerated therapies are needed now to help achieve a greater impact on the future morbidity and mortality of this disease. Meanwhile, the development of initiatives to prevent (i) the further spread of HCV

infection among current IDUs and (ii) the initiation of non-IDUs into injecting should not be neglected.

7.3 Key data required to refine future HCV projection modelling work

Projections clearly rely on the accuracy of the model assumptions used to derive them. As new data become available, improvements in the modelling of the HCV epidemic in Scotland, as elsewhere, will be possible, leading to further refinement in these estimates. The following six sections outline areas for future work related to HCV projections in Scotland.

7.3.1 Scotland-wide data on the incidence and cessation of injecting drug use

The importance of estimates on the incidence and cessation of IDU has long been recognised, yet few attempts have been made to estimate these in the UK. A modified Delphi approach was used to derive these for Glasgow by combining expert opinion with capture-recapture IDU prevalence estimates. Given the wide certainty ranges surrounding experts' consensus on incidence and cessation, likely brought about by the difficulty in quantifying these parameters, other approaches need to be considered to validate these estimates in Glasgow and provide data throughout Scotland.

A lag-correction method has been adapted from AIDS epidemiology to estimate recent trends in the incidence of heroin use in south-eastern England by adjusting reported numbers of heroin users visiting drug treatment agencies for the time lag between onset of heroin use and first treatment request[111]. This approach could similarly be applied in Scotland to estimate the relative incidence of injecting drug use from reports to the Scottish Drugs Misuse Database[121]. This database however only dates back to 1992 and therefore limits estimation with the lag-

correction method to recent trends in injector incidence. Long-term historical data of the IDU epidemic are required to estimate completely the past incidence of HCV in this population.

In Australia, the back-calculation approach, using national data on opioid overdose deaths, has generated estimates of the numbers of people starting to inject heroin between 1960 and 1997[112]. The validity of the back-projection estimates depends on the consistency and completeness of the surveillance data over time. Reports of drugs-related deaths in Scotland increased 4-fold between 1993 (33) and 1994 (139) as a result of an improved system of collecting information on all deaths involving drugs or persons known or suspected to be drug-dependent[344]. Thus, adjusting historical data on the number of drug-related deaths in Scotland for inconsistencies caused by the reporting systems is essential in order to use these data to generate estimates of the incidence of injecting drug use through back-calculation. A study, implemented by SJH, SMB and DJG in 2004, linking SCIEH's national HIV test database with Scotland's deaths register will allow the examination of the vital status of approximately 12,500 Scottish IDUs, who had tested negative for HIV antibodies during 1988-2003, and inform the adjustment of historical reports for misclassification of overdose deaths.

Injecting drug users are a difficult group to follow prospectively, and therefore many studies – usually cross-sectional – of this population are restricted to elucidating short-term changes in injecting behaviour. However, long-term cohort studies measuring the injecting patterns of individuals following commencement of injecting drug use are required to allow accurate estimation of the cessation of IDU, both regionally and temporally, in Scotland. Meanwhile, the estimation of cessation rates may be achieved by combining available data on IDU prevalence and mortality with a

greater understanding of the incidence of injecting drug use, using the simulation methods outlined in Chapter 2.

7.3.2 Mortality among current IDUs

The simplest assumption of a common and constant risk of death was applied among current IDUs (1-2% per annum) in the HCV projection model in Chapter 6 and among heroin users (0.6-1% per annum for overdose death) in back-calculation models estimating the past incidence of injecting heroin use[112]. However, de Angelis et al. have demonstrated the sensitivity of back-calculation estimates to the assumption of a common and constant risk of overdose death[345], and underlined the need for reliably estimated gender and age specific rates.

Relating reported drug-related deaths in Scotland to the prevalent number of current IDUs generated through capture-recapture studies, with assumptions about the age and gender distributions, indicated that these deaths were more common among men (1.7 times more frequent than among females) and those older than 34 years of age (2.1 to 6.6 times more frequent than those younger than 25 years)[152]. Corroboration of these findings is needed from cohort studies of IDUs, which can directly calculate mortality by gender and age. The study proposed above linking the records of approximately 12,500 Scottish IDUs, who had tested negative for HIV antibodies during 1988-2003, to the deaths register provides a relatively cheap opportunity to assess the influence of gender and age at HIV test uptake on drugs related mortality. Scrutiny of the record-linkage data will inform on mortality not only related to drugs but also alcohol and other causes of death.

7.3.3 Alcohol intake of current and former IDUs in Scotland

The meta-analysis in Chapter 5 illustrated a significantly increased risk of cirrhosis (RR 2.3; 95% CI 1.7-3.3) associated with alcohol intake defined in the range of at least 210 to 560g per week. The record-linkage of 12,096 HCV diagnosed positive persons to hospital admission data, presented in Chapter 4, identified alcohol as a factor in 71% of 514 cases developing HCV-related liver failure during 1991-2001 in Scotland. Despite the recognition that alcohol is one of the main predictors of a worsened outcome with chronic HCV, the drinking patterns of IDUs (the group most affected by HCV infection in resource-rich countries) have thus far received little attention. A particular concern is that drug injectors who have been treated for their drug problems may subsequently substitute their illicit drug use with alcohol[346,347].

Studies of drug users receiving drug treatment in England have reported prevalences of either problem drinking or drinking above the recommended safe limits in the range of 15-45%[219,296,297,298]. To accommodate this range of uncertainty in the HCV projection model, outlined in Chapter 6, three rates (0%, 20% and 40%) of heavy alcohol use were explored. Varying disease progression rates according to 40% uptake (versus 0% and 20%) of heavy alcohol use – along with age at HCV acquisition, gender and HIV co-infection – improved the consistency of simulated outcomes with record-linkage results.

Further research is required to determine accurately the prevalence and determinants (e.g. gender, current/former injector status and HCV antibody status) of heavy drinking among IDUs in Scotland. Building upon the record-linkage work developed in Chapter 4, which established that 17% of 12,096 HCV diagnosed persons in Scotland had a history of alcohol abuse resulting in either hospitalisation or death, the same approach could be used to determine the prevalence of alcohol-related

problems among persons presenting for drug treatment in Scotland. The Scottish Drugs Misuse Database (SDMD) holds data on all individuals who have sought treatment for their drug use for the first time ever or in the last six months: including a minimum set of identifiers (i.e. forename and surname initials, fourth letter of surname, date of birth and gender) to enable internal and external linkage of records and information on ever and recent (i.e. last month) injector status to distinguish between non-IDUs, former IDUs and current IDUs. Linkage of the SDMD to hospital discharge diagnoses records will therefore help gauge the alcohol abuse patterns of current and former IDUs by region in Scotland. A limitation, however, of the hospital data is the absence of information on the quantity of alcohol consumed by patients. Surveys of current and former IDUs would aid interpretation of the hospital data by quantifying the alcohol consumption of those who have and have not been hospitalised with an alcohol-related problem.

7.3.4 Progression of liver disease among HCV chronically infected persons in Scotland

The projection model, outlined in Chapter 6, estimated the increasing severity of HCV disease with age among current and former Glasgow IDUs in 2005. The mean prevalence of moderate disease increased from 6% among chronic HCV infected (both current and former) IDUs aged under 30 years to 29%, 47%, and 53% among those aged 30-39, 40-49 and 50 years or more, respectively. Meanwhile, the mean prevalence of cirrhosis increased from 4% among those aged 30-39 years to 9% and 28% among those aged 40-49 and 50 years or more, respectively.

To assess the accuracy of these projection estimates, there is need to collate information on the histological status – together with the patient's age, gender, risk

group of HCV acquisition, health-board of residence, HIV status, and alcohol history – of HCV chronically infected patients in Scotland undergoing liver biopsy. A project initiated by the Scottish Viral Hepatitis Group, funded by the Scottish Executive and currently in the early stages of implementation, aims to collect the above and other key epidemiological and clinical data on HCV infected persons in Scotland who are, or have been, in clinical care to form the Scottish Clinical HCV database. The factors causing patients to present for clinical assessment and undergo a liver biopsy, as discussed in the meta-analysis of Chapter 5, will likely influence the histological results by over-estimating the prevalence of moderate and severe liver disease; these biases would therefore need to be considered when comparing liver biopsy results with projection estimates.

Liver biopsy is internationally recognised as the gold standard for assessment of hepatic fibrosis, as non-invasive markers developed to date are unable to predict reliably the stage of liver disease[348]. The importance of liver biopsy for chronic HCV was highlighted in a recent study that showed a substantial proportion (68%: 25/37) of biopsy proven cirrhosis patients were not identified as cirrhotic through clinical diagnosis[349], which is important since these patients are generally not offered therapy because of concerns over safety and efficacy. Despite this, a recent statement, made at the Consensus Conference on HCV in Edinburgh during April 2004[350], dismissed the role of liver biopsy in the clinical follow-up of certain HCV-infected patients – on the basis of the morbidity and mortality risks associated with biopsy and the impressive response rates (up to 80%) from clinical trials of pegylated combination therapy for some genotypes[351]. The absence of information on stage of HCV disease from liver biopsy, or equivalent markers, may however prove to be a major impediment in

prioritising patients for HCV antiviral therapy and validating projection models of HCV infected persons in Scotland.

7.3.5 Validating record-linkage estimates of the incidence of HCV-related severe disease in Scotland

Knowledge of the number of HCV-infected IDUs developing decompensated cirrhosis each year in Scotland was integral to the fitting of the projection model in Chapter 6. Estimates were based on findings from the record-linkage work, as described in Chapter 4, of the numbers of HCV diagnosed individuals admitted to hospital with decompensated cirrhosis, which were adjusted to account for the proportion associated with injecting drug use (88%) and the non-hospitalisation (14%) and non-HCV-diagnosis (18%) of decompensated cases. The hospital morbidity data alone under-estimated the incidence of severe HCV-disease as 14% of deaths from decompensated cirrhosis among HCV diagnosed persons were not identified with this complication in the hospital register. In addition, the non-HCV-diagnosis rate was taken as the proportion (18%) of hospitalised HCV-related decompensated cirrhosis cases who were not diagnosed with HCV infection until >14 days after their hospitalisation.

Further study of the HCV antibody status of patients presenting with severe liver disease, particularly those with other aetiological factors such as alcohol abuse, is needed to validate the record-linkage results and assess whether or not all HCV-infected cases had been estimated using this approach. Matching the identifiers of patients either presenting to hospital or dying with decompensated cirrhosis and HCC in Glasgow and Edinburgh against local Regional Virus Laboratory HCV test records will establish the HCV test uptake of cases in these regions and inform whether or not

current testing practices are adequate to detect HCV infection among persons with severe liver disease in Scotland.

7.3.6 Determining the most cost-effective approaches to testing and treating IDUs for chronic HCV in Scotland

A total of 43,000 persons, who had ever injected drugs, were estimated to be living with HCV antibodies by the end of 2003 in Scotland (from modelling work presented in Chapter 6), of whom approximately 14,000 (32%) had been diagnosed. Of these HCV-infected IDUs in Scotland, 32,000 were estimated to be living with chronic HCV and therefore at risk of developing cirrhosis. In comparison, relatively few Scottish IDUs have received antiviral therapy (estimated optimistically at 1,500 in the projection model). Progress needs to be made in identifying individuals eligible for antiviral therapy and in retaining those diagnosed with chronic HCV in clinical follow-up.

The concern is that those who would benefit most from an HCV diagnosis – infected persons with moderate hepatitis who do not (or no longer) inject drugs – are not being offered and recommended a test or are lost to clinical follow-up. An evidence-based approach to chronic HCV case-finding is essential if limited resources are to be used effectively in identifying those most in need of antiviral therapy. The modelling presented in this thesis highlighted the potential benefit of targeting HCV testing at former IDUs aged 30-39 and 40-49 years as 16% and 27% of those in Glasgow, respectively, were estimated to have moderate disease in 2005 (32% and 47% of those chronically infected, respectively). Further research is needed to examine the clinical benefits and cost-effectiveness of different HCV testing strategies targeted at former IDUs.

The projection model, designed and calibrated for IDUs in Glasgow, provides the foundation to examine the cost-effectiveness of the latest available treatments for chronic HCV among patient subgroups with different stages of disease and host factors. A key finding from the HCV projection work undertaken for Glasgow was that consistency between model and epidemiological data improved by allowing HCV disease progression rates to depend on age at HCV acquisition, gender, HIV co-infection and heavy alcohol use. Incorporating this heterogeneity in the natural history of chronic HCV into cost-effectiveness models may have important implications for treatment decisions in an evolving patient population.

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