Scottish Needs Assessment Programme

Hepatitis C

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SCOTTISH NEEDS ASSESSMENT PROGRAMME

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PREFACE

Hepatitis C is a rapidly changing field and the remit of this report was ambitious. The group has tried to produce a comprehensive report in a timely manner but accept that there are areas where additional work still needs to be undertaken. The limitations to the data and additional research currently underway are described where appropriate.

The main area where additional work is recommended is in the prevention of continuing transmission of hepatitis C amongst injecting drug users and a national workshop is planned for November 2000.

The report is substantial but it is possible for professionals with specific interests to read the relevant sections in conjunction with the introductory sections, for example:

- Health promotion and primary prevention
- Detection and Diagnosis
- Management

EXECUTIVE SUMMARY

An estimated 35,000 people, 0.7% of the Scottish population, are infected with the hepatitis C virus (HCV), of whom approximately 10,000 are diagnosed. World-wide prevalence is estimated to be 3%. Hepatitis C can affect people's physical, mental and social well being and can reduce their life expectancy. This epidemic is a major public health problem of appreciable proportions.

Hepatitis C affects many groups in our population, not just injecting drug users. The risk of transmitting hepatitis C through contaminated blood and blood products has been addressed in the United Kingdom but transmission is continuing amongst injecting drug users because needles and other injecting equipment are still being shared.

The virus can be transmitted sexually and from mother to child, but the risk is small. The virus can also be transmitted from an infected patient to a health care worker and from a health care worker to a patient but the risk is very small. Health care workers with HCV who have been shown to be associated with transmission of the infection should no longer perform exposure prone procedures.

The key to controlling the continuation of the epidemic is a strategy that aims to minimise sharing of injecting equipment amongst drug users. The aim should be reduction in sharing to zero. As new cases are still occurring amongst injecting drug users at 20-30 per 100 person years the need to address this epidemic is urgent.

Up to 80-85% of those infected with HCV develop chronic hepatitis and this can lead to cirrhosis, liver failure and hepatocellular carcinoma. Only a proportion of those with hepatitis C are suitable for anti-viral treatment (10-40%). Combination therapy, interferon alfa plus ribavirin, is more effective than interferon alone. Of those who are suitable for treatment about 30-50% can expect to sustain a response to treatment with combination therapy but some will drop out because of side effects. Combination therapy, alone, will cost £5,000-10,000 per course of treatment and the additional cost per quality adjusted life year gained is between £7000-36,000.

The main challenge to the health service beyond prevention, detection and appropriate anti-viral treatment is the management of cirrhosis and liver failure. 20% of those infected can expect to have cirrhosis after 20 years and 50% after 30 years. Up to 70% of costs of caring for someone with hepatitis C are incurred during the late stages of the disease and relate to management of the complications of liver failure i.e. ascites, oesophageal varices and hepatic encephalopathy. There could be over 6000 additional patients with cirrhosis associated with hepatitis C by 2009.

The services for the care of patients with hepatitis C in some areas are patchy and have been developed with little strategic planning or identified funding. The report describes the essential components of an integrated service.

The priorities for now are the effective prevention of new cases, and the equitable access to specialist assessment and effective treatment for those with the disease.

RECOMMENDATIONS

Primary prevention

1. A national workshop should be held on the prevention of transmission of hepatitis C amongst injecting drug users in Scotland, sponsored by SNAP and/or the Scottish Executive and involving SCIEH, HEBS, Health Promotion Officers, Scottish Drugs Forum and Scottish Advisory Committee on Drug Misuse. The workshop should review the current preventive measures for hepatitis C in injecting drug users and also identify the most appropriate way to raise awareness of infective risks associated with drug misuse.

   Action SCIEH, SNAP and Scottish Executive

2. Recommendations of this national workshop for the primary prevention of hepatitis C should be adequately resourced. This should not be at the expense of existing prevention activities for other bloodborne pathogens.

   Action Scottish Executive

3. As a matter of urgency all Health Boards should review their current health promotion and primary prevention activity for all bloodborne pathogens pending the outcome of the national workshop. Primary prevention strategies for bloodborne pathogens must be consistent with the drugs strategies.

   Action Health Boards

4. The focus of primary prevention of hepatitis C should be in the drug using population and should include clear and accurate messages about risks of injecting and sharing. Sharing of injecting equipment must be minimised – the aim is reduction to zero.

   Action Health Boards and Drug Action Teams

5. Enhanced needle and syringe exchange schemes with health promotion and primary prevention advice should be considered and adequately resourced. These must be easily accessible and consideration should be given to times of opening, geographical spread and outreach services to target groups early in their drug injecting career.

   Action Health Boards and Drug Action Teams

6. Health care professionals should receive education and training about hepatitis C, its natural history, prevention and infection control, investigation and management, appropriate to their needs.

   Similar education and training should be offered to other occupational groups within the public, private and voluntary sector who work with drug users.

   Action Health Boards, Drug Action Teams and Trusts, plus agencies in the statutory and voluntary sectors

7. Primary prevention must also address other routes of transmission and should include maintaining the optimum screening and treatment procedures for blood and other donations, reducing the risk of sexual transmission, and minimising nosocomial and occupational transmission.

   Action Scottish Blood Transfusion Service, Health Boards and Acute Trusts

8. Consideration should be given to the licensing or regulation of body piercing premises to minimise risks of transmission of infection including hepatitis C.

   Action Scottish Executive

Detection and Diagnosis

9. All high risk groups should be offered counselling, and testing for hepatitis C if appropriate after discussion. Testing for hepatitis C must include the provision of pre and post test discussion by trained individuals in appropriate settings.

Action Health Boards and Acute and Primary Care Trusts

10. The availability and funding of virological investigations for HCV across Scotland should be clarified and adequate resources made available. As yet there are insufficient numbers of HCV antibody positive patients outside the central belt to justify the introduction of HCV PCR testing at other sites, unless the technology can be extended to other diagnostic work.

Action Scottish Executive and Virology laboratories

11. 'Viral hepatitis' is a notifiable disease and the notification system should be revised to differentiate between different hepatitis viruses.

Action Scottish Executive

12. Virology laboratories should report all new cases of hepatitis C to their local Department of Public Health.

Action Virology laboratories

13. Electronic links should be developed between virology laboratories and Departments of Public Health to facilitate transfer of hepatitis C data.

Action Health Boards and SCIEH

Management

14. Each Health Board should have a local policy for detection, referral and management of patients with hepatitis C and must address the significant resource implications associated with providing a service to care for patients with hepatitis C.

Action Health Board and Trusts

15. A lead clinician or clinicians should develop, deliver and co-ordinate appropriate local services to ensure an integrated pathway of care for all patients with hepatitis C, from diagnosis to endstage liver disease. This could be facilitated by the appointment of clinical nurse specialists.

Action Health Board and Acute Trusts

16. All newly diagnosed patients should be offered referral to a specialist and should have access to specialist counselling and advice.

Action Health Board and Primary Care

17. Interferon plus ribavirin is more effective than interferon alone and Health Boards should consider the relative priority of provision of these drugs for their population. The cost effectiveness of the various regimens should be taken into consideration when decisions are made regarding funding of these drugs.

Action Health Boards and Acute Trusts

18. Surveillance programmes for monitoring patients with progressive chronic liver disease for the early detection of hepatocellular carcinoma and oesophageal varices should be established and resourced.

Action Health Boards, Acute Trusts and the Scottish Liver Group

Surveillance and research

19. Epidemiological surveillance must continue to monitor new cases, routes of transmission and changes in prevalence and incidence, disease progression and effect of interventions. An enhanced national register of hepatitis C cases should be established in collaboration with the existing clinical databases so that the natural history of hepatitis C, the impact of treatment and the healthcare resources utilised by infected patients can be monitored.

Action SCIEH, ISD and the Scottish Liver Group

20. Research funds and initiatives should be targeted at hepatitis C and participation in multi-centre trials should be encouraged.

Action Health Boards and Acute Trusts

GLOSSARY

ALTs	Alanine aminotransferases
DNA	Deoxyribonucleic acid
ELISA	Enzyme linked immunosorbent assay
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDUs	Injecting drug users
ISD	Information and Statistics Division
MRC	Medical Research Council
NSC	National Screening Committee
PCR	Polymerase chain reaction
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
SCIEH	Scottish Centre for Infection and Environmental Health
SHPIC	Scottish Health Purchasing Information Centre
SMR	Scottish Morbidity Record
WASH-C	Willing anonymous salivary hepatitis C survey
WHO	World Health Organisation
3MU TIW	Three million units three times a week

1. INTRODUCTION

Hepatitis C infection is a global public health problem. The World Health Organisation estimates that 3% of the world's population are infected with the hepatitis C virus (HCV) and more than 170 million people may have chronic hepatitis C.[1,2] The prevalence in the UK is estimated to be between 0.5% and 1% of the population. This is similar to the estimated prevalence in Austria, Germany and Belgium but less than France, Spain and Italy where the prevalence is estimated to be above 1%. This compares to an estimated prevalence of 1.8% in the United States.[3] The Scottish Centre for Infection and Environmental Health (SCIEH) estimate that there may be 35,000 people in Scotland with HCV (0.7% prevalence).

Concern has been voiced by a wide range of professionals about the implications of hepatitis C for the public's health and the impact on the health service now, and in the future. There has been an increased demand for testing, referral, and treatment affecting a wide range of services. Combination therapy was licensed in 1999 and has significant resource implications for Trusts and Health Boards. There is also concern about the potential increase in the number of patients with liver failure and hepatocellular carcinoma and the subsequent impact on the transplant services, as has been seen in the United States where hepatitis C is now the commonest reason for liver transplant in adults.[4] As with the other bloodborne pathogens, the importance of primary prevention, health promotion and education cannot be overemphasised and this epidemic needs to be addressed now.

There is also increasing concern amongst hepatitis C positive individuals about the lack of a UK national strategy to address the issues. This was clearly voiced at the recent 4th International Conference on Hepatitis C held in London in November 1999. The delegates at this conference included representatives from the British Liver Trust and C Change, the Haemophilia Society, Capital C from Edinburgh and support groups from Glasgow.

In view of these concerns Dr. Andrew Fraser, the Deputy Chief Medical Officer, asked the Scottish Needs Assessment Programme (SNAP) to undertake this needs assessment for hepatitis C in Scotland.

2. AIMS AND OBJECTIVES

- To describe the emerging epidemic of hepatitis C in the Scottish population
- To collate current knowledge on prevention, investigation and treatment
- To describe the current status of services to meet the challenge which hepatitis C presents
- To make estimated projections for implications in the Scottish population and for services to meet the need.
- To make recommendations to meet identified needs.

A multidisciplinary working group was convened to undertake the Needs Assessment drawing on the considerable work already undertaken by Grampian, Greater Glasgow and Lothian Health Boards. A survey of Health Boards was carried out during August/September 1999 to establish current provision of services.

The report was sent out for consultation in April 2000 and the groups invited to comment are shown in Appendix 1.

3. HEPATITIS C - THE NATURE OF THE PROBLEM

Hepatitis C is a slowly progressive, and often silent, disease of the liver caused by HCV. The virus is spread by blood or blood stained body fluids. HCV is a flavivirus with six distinct genotypes plus numerous subtypes, and was first identified in 1989 as a cause of non-A, non-B hepatitis. There is no vaccine for prevention of hepatitis C.

The routes of transmission include:

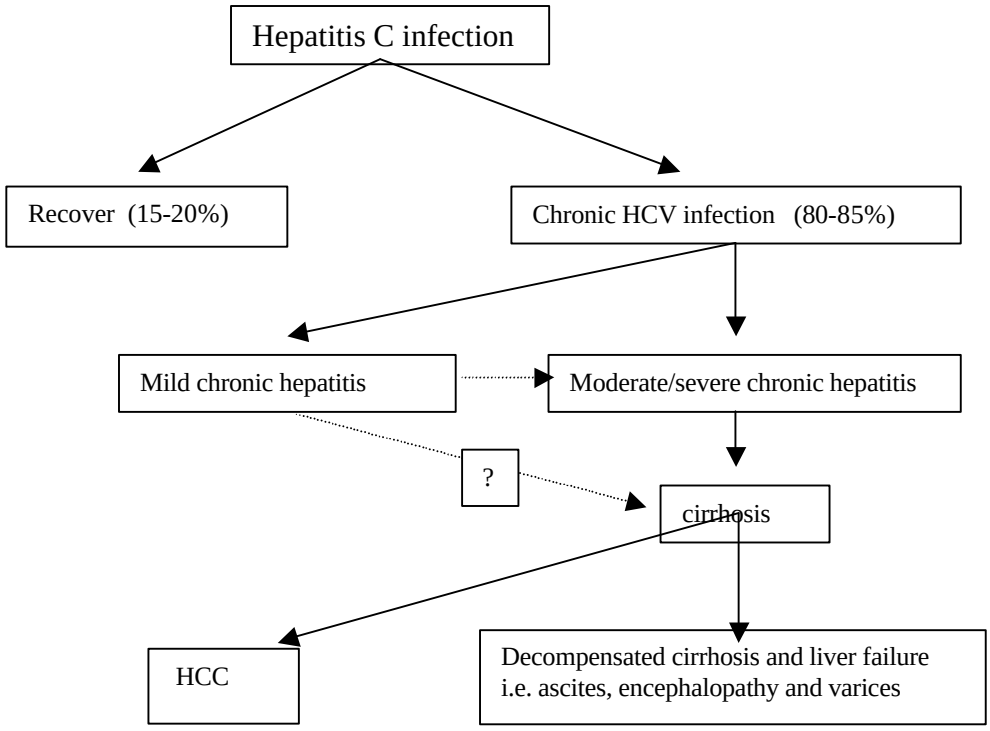
- injecting drug use and the sharing of needles/equipment – the most common route (concomitant HIV infection increases the risk of transmission[5])
- contaminated blood components - platelets, fresh frozen plasma or cryoprecipitate[5,6] prior to introduction of virus inactivation in 1987
- transfusion of contaminated blood prior to the introduction of blood donor screening in September 1991
- unprotected sexual intercourse with hepatitis C antibody positive partner – risk estimated to be less than 5%[7]
- from an infected mother to her child during pregnancy or at the time of birth, 2-5%[8]
- transmission from a patient with HCV to a healthcare worker by a needle stick injury; the risk is about 1 in 30 compared to 1 in 3 for hepatitis B and 1 in 300 for HIV[9]
- tattooing, electrolysis and body piercing - if equipment is contaminated and inadequately sterilised[6]

After exposure to HCV nearly all patients develop raised serum alanine aminotransferase (ALTs) within 7 weeks but the majority are asymptomatic and anicteric.[10] A small proportion of patients develop an acute hepatitis with jaundice, malaise, weakness and anorexia. After acute infection about 15% appear to resolve their infection without sequelae, as defined by sustained absence of HCV RNA and normalisation of serum ALT. [11] (Figure 1)

Patients with chronic infection have chronic hepatitis: around 80-85% have persistent viraemia, detected by current methodology, although some patients who are non viraemic can be demonstrated to have the virus in their liver.[10-13] This high proportion is attributed to the genetic diversity of the virus which allows it to escape host recognition.[11,14] The persistence of the virus in such a large proportion of those exposed creates a large pool of potentially infectious individuals.

Disease progression and severity is very variable and patients may not become symptomatic until their liver disease is advanced.[10] In a French study about a third of those initially infected developed cirrhosis within 20 years.[15] A third of these patients progressed to cirrhosis between 20 and 50 years and a further third progressed extremely slowly or not at all. It is not possible to accurately predict which group of patients will progress at a very slow rate but this study did demonstrate that the disease progresses faster in men, those infected over 40 years old and those with high alcohol consumption.[15] The disease also progresses faster in those co-infected with HIV or hepatitis B. The median time from infection to cirrhosis was 30 years. The estimated annual risk of hepatocellular carcinoma (HCC) in patients with cirrhosis is 1-4% per year[16] and it is rare in those without cirrhosis.[17] Some patients with end stage liver disease or HCC may require liver transplantation.

Figure 1. Disease progression in hepatitis C

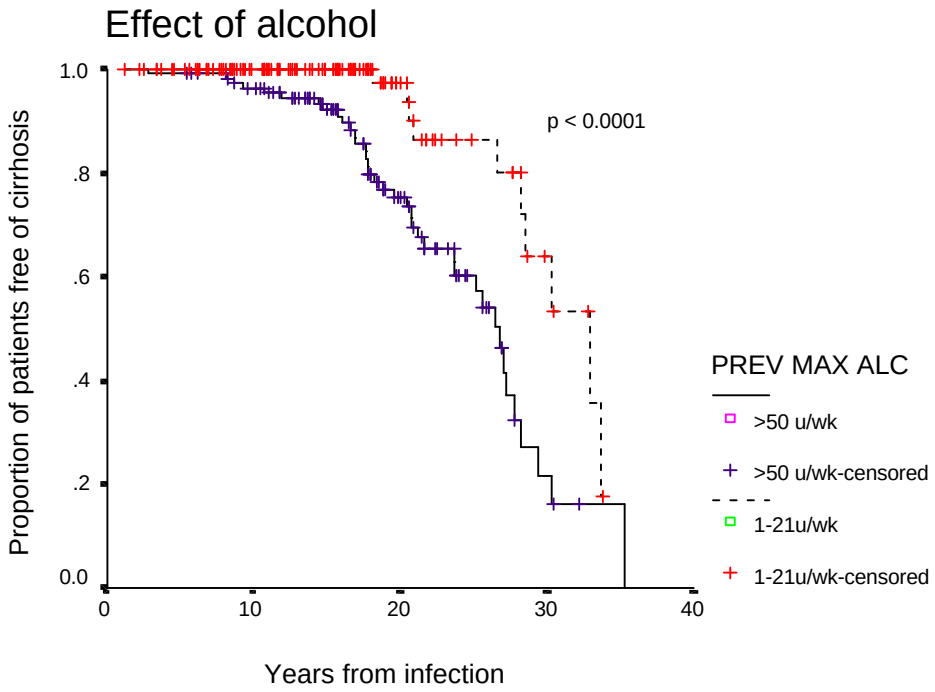


The natural history of patients in Scotland is best described by a study from the Royal Infirmary of Edinburgh, which is the tertiary referral centre for the South East of Scotland.[18] This study comprises 301 patients who presented for assessment including histological investigation and therefore form a highly selected population 70% of the study population were male and the median age at infection was 20 years. 21% of this cohort had progressed to cirrhosis 20 years after infection, 33% after 25 years and 50% after 30 years. The disease progressed faster in those who drank excessively and when the disease had been acquired after age 30. These results are consistent with other retrospective studies. See Figure 2 for a Kaplan Meier graph of progression from infection to cirrhosis over time and the effect of alcohol.

The quality of life for patients with hepatitis C can be markedly reduced even in mild disease. Symptoms do not correlate well with severity of disease.[19] Hepatitis C is also a systemic disease and is associated with cryoglobulinaemia, renal disease, thyroid disease, lymphoma and porphyria cutanea tarda.[16,20]

A recent review concluded that there is only a small excess of morbidity and mortality in the first twenty years after infection but this increases with time, especially in those with cirrhosis.[21] The outcome amongst those patients with chronic hepatitis but no cirrhosis is unclear.[21] A cohort study of 4865 haemophiliacs recently demonstrated an emerging increase in mortality from liver disease and liver cancer in the UK haemophiliac population that could be attributed to HCV infection.[22]

Figure 2. Kaplan-Meier graph of progression from infection to cirrhosis showing the effect of alcohol [23]



Note: Prev. max. alc. – previous maximum alcohol consumption in units of alcohol per week.

This graph is from the database of patients who have attended the RIE and have been investigated. It shows the progression from infection to cirrhosis over time. The faster progression is found in those who had previously drunk more than 50 units of alcohol a week for more than five years and the slower progression is in those who have drunk less than 21 units a week.[23]

4. EPIDEMIOLOGY OF HEPATITIS C IN SCOTLAND

4.1 Prevalence of Hepatitis C

The prevalence rates in published studies vary widely depending on the sub-population studied[1] with the highest reported prevalence amongst haemophiliacs, recipients of contaminated blood and injecting drug users (IDUs). A brief review of prevalence studies from the literature is summarised below plus a summary of studies undertaken in Scotland by SCIEH in collaboration with other researchers.

4.1.1 Blood donors

Scottish blood donors have a prevalence of 0.09%.[24] This is similar to other parts of the UK, e.g. London (0.07%)[25] and North West of England (0.04%)[26] but low in comparison to blood donors in other countries, e.g. USA 0.36%, Italy 0.9%, Australia 0.45%.[27]

4.1.2 Recipients of blood products including haemophiliacs

Prior to 1985 the majority of patients with clotting disorders were exposed to HCV and almost all of these will be HCV antibody positive.[28-30] Most of these patients will still be receiving specialist care and will have been offered testing for HCV but some patients with mild haemophilia or Von Willebrand's disease, who may have been exposed may not yet have been identified. Heat-treated factor VIII has been routinely available in Scotland since April 1987.

4.1.3 Blood transfusion recipients

Prior to the introduction of blood donor screening in 1991 some blood donors who were HCV antibody positive unknowingly continued to donate. In 1995 a major UK lookback exercise was conducted to identify the donations given by HCV antibody positive donors prior to 1991 to trace the recipients and offer them counselling, investigation and treatment if appropriate.

4.2.4 Renal dialysis patients

In 1991, prior to the introduction of blood donor screening, the estimated seroprevalence of HCV in the three Glasgow Renal Dialysis Units was 3.9%.[31] The number of blood transfusions received, and the length of time on dialysis were consistently associated with HCV prevalence. In 1994 an outbreak of HCV was detected in one of the Glasgow units. Transmission took place from two known HCV antibody positive patients when, it is assumed, universal precautions broke down. Four new patients were infected, two from each of the known patients.[32] HCV antibody testing of all new entrants to dialysis units and six monthly screening are now in place. As HCV RNA can be detected for prolonged periods in this patient group, prior to seroconversion, it could be argued that HCV PCR testing of all patients annually would be more effective.

4.1.5 Prevalence of hepatitis C in injecting drug users in Glasgow

Salivary HCV antibody tests were carried out on stored samples from cross sectional studies undertaken in 1990-94,[33] 1996[33] and 1999[34] and the results were adjusted for sensitivity of the test to estimate HCV seroprevalence. All the salivary results below are presented with adjusted seroprevalence results in brackets.

Of 1949 injectors, recruited during 1990-94 and 1996, 61% were salivary antibody positive (72% serum). No gender differences in prevalence were seen but prevalence did increase with length of injecting and with age. For the 195 injectors recruited in 1996, the prevalence was 56% (66% serum). In 1999, the HCV antibody positive

prevalence among 468 injectors who had commenced their injecting since 1990 was 45% (53% serum).

Unlinked anonymous HCV antibody testing of sera from Glasgow injectors who underwent a named HIV antibody test during 1995-97,[35] gave a prevalence of 74%. Thus the prevalence in this selected population was similar to those seen in the voluntary anonymous community-wide surveys.

4.1.6 Prevalence of hepatitis C in injecting drug users in the rest of Scotland

Unlinked anonymous HCV antibody testing of sera from injectors who had undergone named HIV testing gave prevalences of 47% in Edinburgh in 1995-97, 64% in Dundee in 1995-96 and 37% in Aberdeen in 1996.[36]

Seventy-one per cent of injecting females who were recruited into an HIV heterosexual transmission study in Edinburgh during the 1980s were HCV antibody positive.[37]

Small community-wide surveys of injectors gave prevalences of 16% in Ayrshire and Arran in 1996, 38% in Lanarkshire in 1997 and 20% in Argyll & Clyde in 1996.[34] These results should be interpreted cautiously because of the surveys' small sample sizes.

Overall prevalence of hepatitis C among IDUs in Aberdeen, Dundee, Edinburgh and Glasgow in 1995/1996 was 62% (1173/1905).[36]

4.1.7 Prisons - Willing Anonymous Salivary Hepatitis C surveys

These surveys provide recent HCV antibody prevalence data on injecting populations in five Scottish prisons during 1994-96.[38] Overall prevalence among inmates who reported ever injecting was 49% (58% serum). Virtually all the injector inmates who were in Low Moss, Barlinnie and Cornton Vale Prisons were from Glasgow or its surrounding areas, while those from Perth and Aberdeen Prisons were from Tayside and Grampian respectively.

4.1.8 Prevalence of hepatitis C in injecting drug users in England

The few HCV antibody prevalence studies that had been performed in England before 1998 all involved the recruitment of injectors from 'convenience settings'. HCV antibody prevalence among injectors attending drug treatment/advisory services was 51% in East Anglia,[39] 68% in Newcastle[40] and 56% in Liverpool.[41] Since 1990, unlinked anonymous HIV and hepatitis B testing has been performed on saliva from injectors who attended selected drug treatment and needle/syringe exchange centres throughout England and Wales. HCV antibody testing was introduced in 1998, and HCV antibody prevalence was 35% overall, 52% in London and 31% in the rest of England and Wales.[42] No gender differences were observed**.** As expected, prevalence increased with age from 6.7% (14/210) in those under 20 to 58% (485/834) in those aged over 35.

4.2 Incidence of hepatitis C

4.2.1 Incidence of HCV infection among IDUs in Glasgow and Edinburgh

A prospective cohort study is the traditional way to measure incidence and such studies have been performed among injecting populations but not in the UK. They are difficult and expensive to conduct, requiring the recruitment and follow up of an HCV antibody negative cohort. Also, this approach is susceptible to bias since cohorts, invariably, are surveyed in drug and medical treatment settings where it would be unethical not to provide advice on how to help participating injectors prevent themselves becoming infected with bloodborne viruses.

In Scotland, two indirect approaches to estimating incidence have been used; both involve the analysis of data from cross-sectional surveys. The first involves analysing the prevalence of HCV positive antibodies in injectors by the date of commencement of injecting. The second involves the monitoring of changes in HCV antibody positive prevalence over time.

4.2.2 Cross-sectional surveys using time of commencement of injecting drug use

Among the Glasgow injectors recruited into cross-sectional surveys during 1990-94 and 1996,[33] there was a slight, but not significant, decrease in HCV antibody positive salivary prevalence from 67% in 1990 to 56% in 1996. Year of commencement of injecting, adjusted for length of injecting career, was highly predictive of HCV antibody positivity. Respondents who began injecting between 1988-1992 and those who began injecting after 1992 were significantly less likely to be HCV antibody positive in saliva than individuals who commenced their injecting prior to 1988. These data suggest a reduction in the incidence of HCV in Glasgow injectors during the era of needle and syringe exchange in the 1990s. However, the HCV antibody positive salivary prevalence of 31% (36% serum) in those who began to inject after the establishment of needle and syringe exchange in Glasgow in 1992, and who had a mean injecting career of only one year, indicates that HCV continues to spread among injectors.

Analysis of data from the 1999 community-wide cross-sectional survey[34] provides further evidence that HCV continues to be highly incident in this group; 44% (51% serum) of 151 injectors who had commenced their injecting since 1996 were antibody positive.

Similar data is available from the Willing Anonymous Salivary Hepatitis C (WASH-C) surveys, performed in five Scottish prisons during 1994-96.[38] Of the 114 injector inmates who commenced injecting after 1992, 31% (37% serum) were HCV antibody positive. The estimated incidence of HCV per 100 person years of injecting among this group was 20.

4.2.3 Cross-sectional surveys using serial HCV antibody prevalence data

Incidence of infection can also be estimated from serial data from the unlinked anonymous surveys of HCV antibodies in sera from injectors in both Glasgow and Edinburgh.[35]

Between 1989/90 and 1997 in Edinburgh there was a significant reduction in prevalence, from 69% to 13% in those under the age of 25. For those aged 25 and above a similar significant trend was observed from 80% to 54%. Among injectors in both age groups, prevalence decreased significantly between 1995 and 1997. Among those aged 15-19, prevalence decreased significantly from 32% in 1989/90 to 14% during 1995/97.

In Glasgow, a similar reduction was observed in those aged under 25, from 91% in 1990 to 43% in 1997. For those aged 25 and above, however, no significant reduction was observed. Among those aged 15-19, prevalence decreased significantly from 92% in 1990 to 21% during 1995-97.

The significant reductions in HCV antibody positive prevalence in younger injectors in both Edinburgh and Glasgow suggest that there has been a steady, continual, decrease in the incidence of HCV among this group during the era of needle/syringe exchange, methadone maintenance therapy and other interventions which were introduced from the late 1980s onwards to reduce the spread of HIV infection. The differences in changes in prevalence suggest that the decline in the incidence of HCV may have started earlier in Edinburgh than in Glasgow. However, with 17% of 15-19 year-olds in both cities, sampled during 1995-97, being HCV antibody positive, infection was still occurring among injectors who had only recently begun to inject.

4.2.4 Other indicators of HCV incidence and risk behaviour

Elsewhere in Scotland, there are no similar data to indicate the direction in which HCV incidence among injecting populations is moving. However, there are some pointers which suggest that incidence may well have increased in recent years. Outbreaks of hepatitis B infection among injecting populations in Inverclyde and in Aberdeen have been observed recently and, in Lanarkshire, infectious disease clinicians have found increasingly high rates of antibody positivity among injectors undergoing named HCV antibody testing.

Behavioural data from the cross-sectional survey of Glasgow injectors in 1999[34] also reveal that the sharing of all types of injecting equipment remains a problem. 44% of respondents indicated that they had injected with a used needle and syringe in the last six months, with 11% on at least a weekly basis. When preparing heroin for injecting, 62% had shared a filter, 70% a spoon and 62% water during the last six months. In 1998/99 32% of injectors who had been registered with the Drug Misuse Database[43] reported that they had shared their injecting equipment in the previous month, a slight increase from previous years. A further 28% reported ever having shared, but not in the previous month.

There is, as yet, no scientific evidence to support the hypothesis that the sharing of injecting equipment other than needles and syringes results in HCV transmission. However, since HIV has been shown to spread this way and since the prevalence of HCV among injectors is far greater than that for HIV, it is highly plausible that such practices could result in transmission of HCV.

4.2.5 Prisons

Analysis of data from the cross-sectional surveys of Glasgow injectors during 1990-94 and 1996,[33] did not indicate that infections were occurring predominantly in prison settings. An HCV incidence study, currently being conducted in HMP Shotts in central Scotland, and funded by the Chief Scientist Office, will inform us of the extent of HCV transmission in a long-stay male prison.

4.2.6 Conclusion

The decline in the incidence of HCV among Edinburgh and Glasgow injectors during the 1990s and the existence of comprehensive harm reduction measures during this period is a temporal association. Nevertheless, in the context of data which suggest that needle/syringe exchanges and methadone programmes in the two cities have led to a decrease in the frequency with which injectors share injecting equipment, the association

is likely to be one of cause and effect. There is no room, however, for complacency. The incidence of infection among injectors, particularly those from Glasgow, remains high at around 20-30 per 100 person years.

4.3 Other routes of transmission in Scotland

4.3.1 Sexual Transmission of HCV

Various studies performed throughout the world indicate that HCV is not easily transmitted through sexual intercourse. Three studies have provided data to gauge the extent of the sexual spread of HCV in Scotland.

- Cohort study of sexual partners in Edinburgh who were discordant for HCV infection.[44]
- Unlinked anonymous HCV antibody testing of residual syphilis serology specimens taken from attendees at genito-urinary clinics in Glasgow, Edinburgh, and Aberdeen during 1996/97.[35]
- Unlinked anonymous HCV antibody testing of residual specimens from pregnant women in Dundee, which had been originally sent to the virus laboratory for routine serological testing in 1997.[35]

The unlinked anonymous testing studies support the view that HCV can be acquired through sexual intercourse but, for most people, the risk is extremely low. Of particular note is the observation that the prevalence of HCV among homosexual/bisexual male genito-urinary medicine clinic attendees is no greater than that for non-injecting heterosexual male attendees. The cohort study revealed no evidence of sexual transmission. In Scotland, those likely to be most at risk are the non-injecting, and the injecting, sexual partners of injectors.

4.3.2 HCV transmission between health care workers (HCW) and patients

There have been only four reported instances of HCW to patient transmission of HCV.[45] In Spain, a cardiothoracic surgeon infected five patients, in England, one patient acquired HCV from a cardiothoracic surgeon and, recently, a woman acquired the virus from a gynaecologist.[45,46] A further lookback exercise was undertaken in Birmingham in June 2000 following identification of a hepatitis C antibody positive HCW.[47]

Several reports, mainly from the USA and Italy have indicated that patient to HCW transmission is not uncommon and the risk of an HCW becoming infected after sustaining a percutaneous injury from a sharp that had been used on an HCW infected patient is estimated to be about 3%.

The prevalence of HCV among in HCWs in England is estimated to be between 0.20%-0.28%.[48,49] These data were generated through small studies of stored, anonymous, samples which originated from hepatitis B immunisation programmes. A similar study of 10,654 HCWs in Glasgow, where the prevalence of HCV among the hospital patient population is known to be appreciable, gave a prevalence of 0.28% with no significant difference between those performing exposure prone procedures (0.23%) and those not (0.27%).[50] It is possible that percutaneous injuries sustained by Glasgow HCWs have become infrequent in the last 10-15 years but no data exist to test this hypothesis. Regardless of the factors responsible for the low prevalence of HCV among HCWs, the findings from this study are reassuring.

At present, the UK Advisory Group on Hepatitis does not recommend routine testing of healthcare workers. Current guidance in the United Kingdom recommends that HCWs

with HCV who have been shown to be associated with transmission of the infection should no longer perform exposure prone procedures.[51] This advice is kept under constant review.

4.3.3 Mother to child transmission

No mother-to-child transmission studies have been performed in the UK but data from elsewhere indicate that the rate of transmission is approximately 5%.[52] Infection appears to be transmitted either in utero or at the time of birth, but not through breast-feeding. In Scotland one study has been performed to determine the prevalence of HCV among childbearing women.[35] In Dundee in 1997, 0.7% of antenatal clinic attendees were HCV antibody positive. It is likely, therefore, that one of the babies born to the 18 women, was infected with HCV. If the prevalence of 0.7% observed in Dundee was typical of that existing elsewhere in Scotland, an estimated 21 HCV-infected babies would be born annually.

4.4 Surveillance of known hepatitis C antibody positive cases in Scotland

SCIEH, in association with the principal hepatitis C testing laboratories, has established a database of all diagnosed HCV infected cases in Scotland.[53] Between 1991 and 1998, 8,075 persons in Scotland had been diagnosed as being HCV antibody positive.[54] Cases are classified by area of residence or by Health Board area of test if information is not available. Some Health Board with prisons in their area may appear to have a higher rate of cases diagnosed than expected.

- 68% (5539) were male.
- 86% (6,918) were aged between 15 and 44
- 9% (732) were aged between 45 and 69
- 2% (172) were aged 70 or over.
- 75% of cases were from Greater Glasgow, Lothian, Grampian and Tayside.
- 2130 cases were diagnosed in 1998- the highest annual number ever
- 44%(944) of these newly diagnosed live in Greater Glasgow.

At December 1998 approximately 1 in 600 people in Scotland were known to hepatitis C antibody positive and the number of unknown cases is likely to be much higher. Preliminary analyses indicate that a further 2000 cases of HCV infection were diagnosed in 1999.[35]

Table 1. Number and rate of diagnosed cases of hepatitis C by Health Board 1991-1998 (excluding children under 5 and unconfirmed positives).[54]

Health Board	Number of known positive cases	Rate per 100,000 population mid year estimates June 1997	% of total number of cases
Argyll and Clyde	444	103.42	5%
Ayrshire and Arran	262	69.59	3%
Borders	54	50.85	<1%
Dumfries and Galloway	112	76.04	1.4%
Fife	195	55.97	2.4%
Forth Valley	336	121.92	4%
Grampian	852	161.24	11%
Greater Glasgow	2893	329.80	37%
Highland	156	74.78	2%
Lanarkshire	438	77.99	5%
Lothian	1518	196.76	19%
Orkney	8	40.32	-
Shetland	14	60.82	-
Tayside	696	177.62	9%
Western Isles	3	10.62	-
Scotland	**8075**	**157.64**	**100%**

Of these 8075 diagnosed cases since 1991 the risk factors were identified as follows

- 53% (4,307) were known to have injected drugs
- 4% (317) were associated with receiving blood factor
- 5% (371) were in the 'other' category – this includes sexual contact, tattooing/body piercing, needlestick injury, bite, blood spillage, blood transfusion and perinatal risk

No information was available for the remaining 38% (3,080) cases. Since 75% (2,315) of the 3080 cases were aged between 15 and 44 years - the age range within which most of the identified injecting drug users belonged - it is likely that the majority of these will have become infected through injecting drug use. If we assume that two-thirds of the 3080 cases for whom no information was available had injected drugs, the overall number of injectors who had been diagnosed as HCV antibody positive would be 6,339 (4,307+2,032); thus 78% of all known infections would have occurred among injecting drug users.

4.5 Total prevalence of hepatitis C (known and unknown)

4.5.1 Injecting drug users

Our best estimate of the prevalence of HCV antibody positive individuals among injecting drug users throughout Scotland is 62%.[36] It is estimated that there are approximately 20,000 current injecting drug users in Scotland[34] and an unknown number of past injectors; thus, an estimated 12,400 current injectors will be HCV antibody positive. Currently, models are being developed by SCIEH to estimate the number of past injectors who are living in Scotland, but these have not yet been completed. In the absence of evidence-based estimates, a range of possible numbers of HCV antibody positive past injectors can be generated if we assume the total populations of living past

injectors to be 10,000, 20,000, and 30,000. However, it is possible that the size of the past injector population is greater than 30,000. Applying the 62% prevalence rate to these estimates of past injectors gives 6,200, 12,400 and 18,600 antibody positive cases. Thus, the total number of prevalent past and current HCV antibody positive injectors would range from 18,600 (12,400 plus 6,200) to a central estimate of 24,800 (12,400 plus 12,400) to 31,000 (12,400 plus 18,600). If the central estimate of 24,800 is accurate, approximately 18,461 antibody positive persons remained undiagnosed as at December 1998 (24,800 minus 6,339 (see section 4.4)).

4.5.2 Non Injectors

Table 2. Estimates of the Prevalence of HCV antibody positivity among high and low risk populations in Scotland, 1996-98

Injecting drug users	620/1000
Heterosexual males attending genito-urinary Clinics (non-injectors)	8/1000
Homosexual/bisexual males attending Genito-urinary clinics (non-injectors)	7/1000
Heterosexual females attending genito-urinary clinics (non-injectors)	3/1000
Pregnant Women (non-injectors)	4/1000
Health Care Workers (including injectors)	3/1000
New Blood Donors*	1/1000
Repeat Donors*	0.06/1000

*injectors asked not to donate but sometimes slip through

Table 2 above shows HCV antibody positive prevalence rates for different population groups in Scotland during 1996-98. Excluding injecting drug users, the highest prevalence was seen in non-injecting heterosexual males who attended genito-urinary clinics (8/1000) and the lowest was observed in repeat blood donors (0.06/1000). On the basis of these limited data which apply, generally, to individuals aged 15-54, an overall prevalence of 1-3/1000 among Scotland's non-injecting population would be plausible. This rate would equate to 5000-15000 antibody positive non-injectors in Scotland.

4.5.3 Injectors plus non-injectors

If we add the central estimate for the non-injectors (10,000, range 5,000-15,000) to the central estimate for the injectors (24,800, range 18,600 – 31,000), the estimated number of HCV antibody positive persons in Scotland would be 34,800, (0.7% prevalence for Scotland). The range would be 23,600 (18600 + 5000) to 46,000 (31000 + 15000).

4.5.4 Estimating the future incidence of HCV-related disease

The essential ingredients of a model to estimate the future incidence of HCV-related liver disease are

- estimates of the incidence of infection over the previous decades especially estimates among injecting drug users
- estimates of the incubation period of HCV infection from the time of its acquisition to the presentation of, for example, cirrhosis and/or liver failure
- the impact of antiviral therapy in preventing HCV disease progression.

Models are currently being prepared but, as yet, are incomplete.

In the absence of evidence-based estimates, a crude estimate of the number of persons who might go on to develop cirrhosis of the liver can be generated. Let us assume that

- 34,800 HCV antibody positive persons are currently alive (central estimate above)
- infection, on average, occurred ten years ago (1989)
- the rate of progression to cirrhosis is 20% within 20 years of infection
- 5% of cases will die prematurely of non-HCV-related conditions.

Since relatively few people are receiving antiviral therapy at present and since the long-term impact of treatment is still uncertain a factor for treatment effect is not included. Thus, by the year 2009 there could be an estimated 6,600 additional cases of cirrhosis as a result of hepatitis C infection (95/100 x 34,800 x 20/100).

5. SERVICES FOR HEPATITIS C – SUMMARY OF THE CURRENT SITUATION ACROSS SCOTLAND

Care of patients with hepatitis C is provided by a wide range of professionals from many different disciplines including health promotion, primary care, the drugs 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. As a result it was not feasible to undertake a detailed assessment of the services in place across Scotland. Each Health Board will need a good understanding of all its own services to inform any service developments.

A questionnaire was sent out to all Health Boards during August and September 1999 to establish an overview of existing service provision and to identify some of the common issues. A full report of the survey is included in Appendix 2 but the main points are summarised below. This represents the information reported in the questionnaire and may be incomplete or fail to reflect the true situation in each Board area.

There is no national strategic framework for hepatitis C in Scotland. The survey results suggest that services provided for prevention, detection and management of chronic hepatitis C in some health board areas have developed in an ad hoc manner with little strategic planning or identified funding. Several Boards are currently drafting strategies for hepatitis C or bloodborne viruses.

The data available from national surveys and surveillance through SCIEH is improving in completeness and accuracy but local information flow between laboratories and clinicians to departments of public health is often poor.

'Viral hepatitis' is a notifiable disease, and although this does not discriminate between the different viruses causing hepatitis, there is a medical responsibility to notify. There is no framework to facilitate the transfer of information from virology to public health.

The primary prevention provided included general health promotion initiatives, harm reduction, needle exchange, services for drug users, training programmes for health care workers and needlestick policies. Only one mainland Board has produced a draft strategy for the prevention of all bloodborne viruses.

Most Boards report that pre and post discussion does accompany HCV testing but it is carried out by a wide range of professionals in primary and secondary care and little is known about what is discussed. The clinical services that exist are delivered by a wide range of specialists in a variety of clinical settings. Only one area has a dedicated service for hepatitis C patients and only three areas have clinical nurse specialists.

6. HEALTH PROMOTION AND PRIMARY PREVENTION

The overall aim is to reduce the number of people exposed to the virus and this includes the general public, patients and professionals. This requires a broad approach and includes measures that address the wider determinants of health and more specifically drug misuse. 'Towards a Healthier Scotland' acknowledges this link with life circumstances and lifestyles but this report will focus primarily on the specific preventive activities that need to be in place or enhanced.

Current and future injectors and their sexual partners are the largest population at risk of acquiring HCV in Scotland. Health promotion initiatives should target both the general public and drug users before they are exposed to risk-taking behaviour. The new Scottish drug misuse strategy 'Tackling Drugs in Scotland – Action in Partnership' acknowledges the health risks to individuals and communities and encourages Drug Action Teams to implement a range of measures to reduce the transmission of hepatitis C including prevention, education and treatment for drug misuse. Any local strategy developed for the prevention of hepatitis C must link with local Drug Action Team's strategy. Many of the health promotion initiatives will be common to all bloodborne viruses and any hepatitis C strategy must be consistent with national and local strategies for the other bloodborne viruses.

Health promotion should be provided by suitably trained individuals who have developed and maintained their skills and knowledge and will include activities that will

- tackle health inequalities, social exclusion and the wider determinants of ill health
- be focused on a general lifeskills approach
- involve parents and the wider community in drug awareness
- foster a positive environment to discuss potentially marginalised behaviour
- provide easy access to well written/easy to understand information
- be developed in partnership with all key players including the health service providers, education authorities, social work services, voluntary agencies, prisons, communities and employers. People who are living with hepatitis C and their families should be encouraged to contribute to the development of health promotion initiatives.

Epidemiological studies undertaken in Edinburgh and Glasgow show that although the incidence of HCV has decreased during the era of needle and syringe exchange schemes the transmission of HCV is still occurring within the drug using population despite existing strategies. Recent data from Glasgow shows that up to 50% of new injectors may be antibody positive. Nationally 32% report sharing in the last month and a further 28% report ever sharing.[43] In Glasgow 44% of injectors reported sharing in the last 6 months and up to 70% reported sharing other items including filters, spoons and water in the last 6 months. Recent outbreaks of acute hepatitis B in Inverclyde and Aberdeen also indicate continuing risky behaviour. There is no scientific evidence that HCV can be transmitted through works other than needles and syringes but it is plausible as HIV can be transmitted this way and the relative index of infection (transmission x carriage) is much higher for HCV.

There may be 12,400 current injectors in Scotland who are HCV antibody positive and the potential for continued transmission of HCV with this level of sharing is enormous. Sharing may not be seen as risky because of the falling incidence of IDU-related HIV in Scotland and the impact of the AIDS health promotion message is fading. Sharing of injecting equipment must be reduced.

Health promotion/primary prevention activity will need to address the specific needs of groups at high risk of exposure to the virus and the essential elements are listed below. Many Health Boards will have some or all of these in place but in the light of the continuing transmission it would timely for Boards to review their policies and to assess the effectiveness of the strategies that are already in place.

- Provision of information, advice and support to reduce the progression of drug users to injecting; this is integral to the drug strategies.

- Harm minimisation and harm reduction messages for all drug users as early as possible in their drug taking career as HCV infection is often acquired soon after commencement of injecting. The potential benefits of using targeted outreach or user led peer education should be explored as a vehicle to reach the drug using population.

- Provision of advice and information to drug users on access to specialist services.

- Education and training of staff to ensure delivery of accurate advice and information.

- Provision of treatment programmes for substance misuse. Methadone and other substitute prescribing, as part of a shared care scheme, are an integral part of treatment programmes to support opiate dependent drug users who wish change their behaviour and reduce their risks.

- Provision of accurate messages about sharing of all equipment - **'Do not share any equipment needles, syringes, filters, spoons or water.'** Needles and syringe packs could be used to target health promotion messages. Professionals and users may have a different understanding of the meaning of 'sharing.' For example sharing may be interpreted as just needles or may not include sharing with a long-term partner or occasional sharing. '**Sharing means sharing with anyone – stranger, brother, sister, parent, husband, wife or partner.'**

- Equitable and accessible needles and syringe exchange schemes with counselling. These must be easily accessible and consideration should be given to times of opening, geographical spread and provision of services to target groups early in their drug injecting career. Again this will be integral to the drugs strategy but should urgently be re-examined to address the continuing transmission of HCV. Consideration should also be given to provision of other paraphernalia associated with injecting drug use e.g. spoons, filters and citric acid, but this would require a change to the Lord Advocates guidance.

- Safe disposal of used needles and syringes.

- Hepatitis B immunisation is recommended for drug users, as there is an increased risk of disease progression with co-infection with hepatitis B and C.[55]

- Hepatitis A immunisation is also recommended in those with chronic liver disease and in haemophiliacs. Hepatitis A may be more severe in these circumstances.[55]

Primary prevention measures must also address other routes of transmission, however small the risk. These include maintaining optimum screening and treatment procedures for blood and other donations, reducing the risk of sexual transmission, minimising

nosocomial and occupational transmission and the risks associated with other percutaneous routes e.g. body piercing and tattooing.

- Screening of all blood, plasma, and organ tissue and semen donations.
- Heat inactivation of plasma derived products.
- Minimising sexual transmission by provision of accurate advice to those at risk. Risk is small but can be reduced by using barrier protection in discordant partners.
- Education and training of health professionals and other professionals in a variety of settings in the public, private and voluntary sectors to minimise risk to themselves and others.
- Implementation and maintenance of infection control procedures in public, private and voluntary sector.
- Education of new staff and re-education of existing staff about specific infection controls in haemodialysis units.
- Regulation and/or licensing of body piercing premises and complementary therapy centres to ensure implementation and maintenance of infection control measures.

The pool of infection and risk of transmission must be reduced within the population by adopting health promotion and primary prevention measures that prevent people starting to use drugs, assist them to stop, prevent them progressing to injecting and then sharing any equipment. This was the main area where the SNAP working group has recommended that additional work be undertaken. A workshop is planned for November 2000 to consider the evidence of continuing transmission, the effectiveness of current strategies and what action can be taken to reduce transmission amongst injecting drug users. Issues for discussion may include

- provision of other paraphernalia associated with injecting drug use
- approaches to behavioural change
- age group to target
- raising awareness of general public and drug users and suitable approaches.

7. DETECTION AND DIAGNOSIS

The overall aim of early detection is the identification of those infected with HCV to allow assessment of their liver disease, appropriate management, consideration for antiviral therapy, advice on how to prevent further liver damage and minimise transmission to others. Identification of people at risk of HCV infection provides the opportunity to discuss risk reduction and HCV antibody testing.

7.1 Virological tests

Diagnostic antibody tests for HCV became available in 1989. The evolution from first to third generation antibody assays resulted in increasing sensitivity and specificity and third generation assays are now widely used in the UK. The diagnosis of HCV infection is made on the basis of a blood test that detects antibody to HCV virus in an enzyme linked immunosorbent assay (ELISA). Reactive specimens are retested in a supplemental assay such as the recombinant immunoblot assay (RIBA).

Molecular assays can be used to detect, quantify and determine the genotype of the HCV RNA in infected patients. Qualitative polymerase chain reaction (PCR) detects viral RNA/viraemia. Viral load is determined by quantitative PCR or by branched chain DNA tests.

Sequencing the HCV genome and comparing selected regions using computerised mapping technologies has led to the recognition of 6 major genotypes of the virus and an increasing number of subtypes, which show a geographical distribution. Types 1,2 and 3 are found in the UK. Genotyping, and to a lesser extent HCV viral load, is used to predict response to treatment and select treatment regimens.

The initial screening test with ELISA is provided by local laboratories but most confirmatory testing is provided by either the Regional Virus Laboratory at Gartnavel Hospital in Glasgow or the Regional Virus laboratory at the City Hospital in Edinburgh. Samples are sent to specialist testing laboratories because facilities for RIBA and PCR are not available locally but these tests are not funded under a nationally agreed contract. There is a long standing arrangement with Edinburgh clinicians to send their samples to a non NHS Research Laboratory at Edinburgh University, and the results may not be known to the Regional Virus Laboratory in Edinburgh. The laboratories providing the service should receive the funding to allow them to meet the increased demand from across Scotland.

There has been a huge increase in demand for HCV testing both serological and molecular. In order to cope with this increase in workload consideration should be given to an alternative approach to diagnosis. Instead of demonstrating the presence of HCV antibody on the first specimen the emphasis should be on identifying patients who carry the virus and are at risk of liver disease. (Figure 3 for proposed HCV testing algorithm). By testing all ELISA reactive specimens for HCV PCR there are a number of important benefits. The result gives the patient and health care professional a more informative result with respect to transmission risks, disease prognosis and treatment needs. If a patient only attends for one test it can be argued that they should have as much information as possible which may lead to alteration in risk behaviour. There may be a reduction in clinic visits, as currently a patient has to attend at least three times for an antibody test and then a HCV PCR test. The change of emphasis from antibody testing to RNA testing should lead to faster laboratory turn round times as staff carrying out a large number of antibody assays can be redeployed to carry out the molecular assays. The increased numbers of HCV PCR tests should also reduce the costs of the tests,

assuming that the current practice of PCR testing is maintained i.e. the testing is carried out at the two Scottish Regional Virus Laboratories. This will also lead to equity of service across Scotland as some health board areas with small numbers of HCV antibody positive patients are already testing all of these patients by HCV PCR at diagnosis.

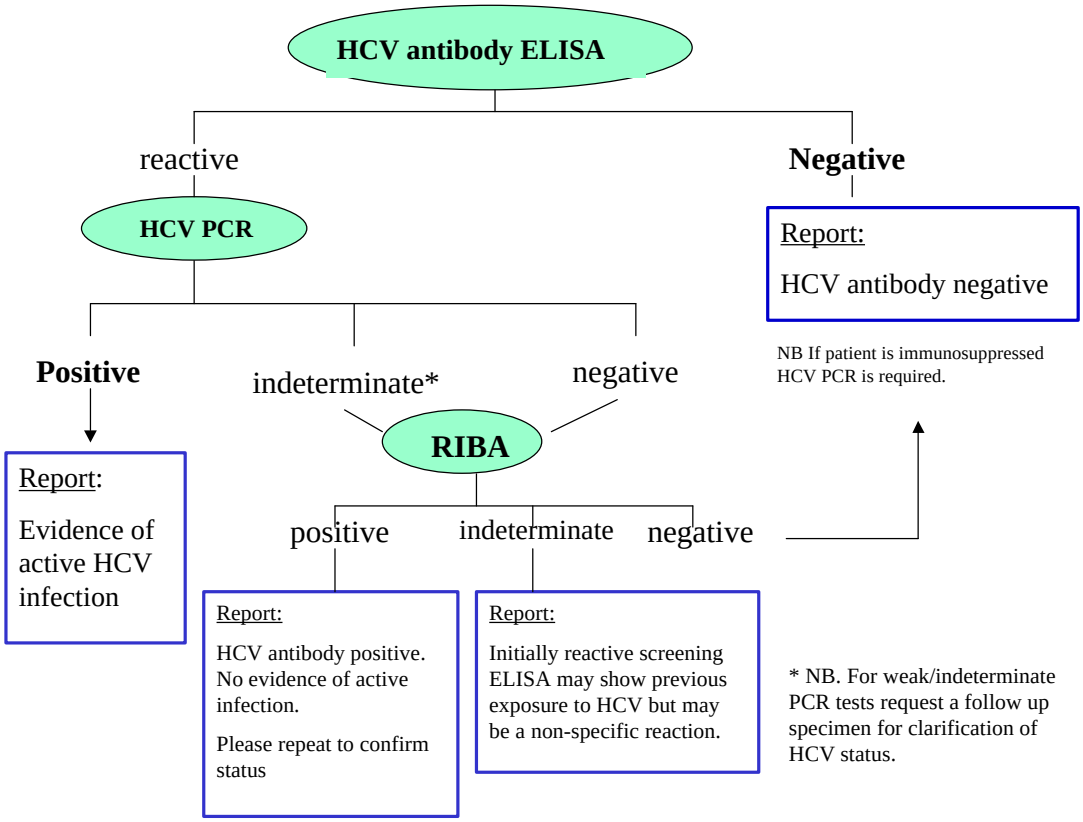


Figure 3. HCV testing algorithm

False positive HCV PCR tests can occur, but repeat testing either at the referring centre or the specialist clinic will help to minimise this problem. Negative PCRs in patients who are RIBA positive should be interpreted with caution and the PCR test should be repeated, and then repeated annually because of increasing sensitivity of the test and other potential sites of viral replication. There must also be good training for health care professionals so that the results are correctly interpreted.

Genotyping and quantitative PCR are available at specialist testing laboratories but at present the demand is low. This will change as new treatment protocols are implemented.

7.2 Who should be tested?

Individuals in high risk groups should be counselled and offered testing if they are considered to be at risk of having hepatitis C, but only after pre test discussion.

People at risk of HCV infection include:

- those who have ever injected illicit drugs
- recipients of blood clotting factors prior to 1987
- recipients of blood products before 1991
- patients on chronic haemodialysis
- patients with persistently abnormal alanine aminotransferase
- healthcare professionals after exposure to HCV positive blood – after full risk assessment
- children of HCV positive mother – antibody testing at one year i.e. once maternal antibodies have declined

Other groups who may be at increased risk of hepatitis C infection may be offered testing, after full discussion of the implications. These include:

- people with tattoos or other body piercing where standard infection control procedures may not have been followed
- sexual partners of HCV positive persons
- people with a history of multiple sex partners or sexually transmitted diseases
- people who specifically request a test – some people who may not admit to any risk factors for HCV infection may have hidden risk factors and their request normally should be respected

Testing for hepatitis C is not recommended for the following groups unless they have other risk factors for infection:

- household (non-sexual) contacts of HCV positive persons
- pregnant women
- general public

7.3 Pre and post test discussion

All those offered testing or requesting a test should have confidential pre and post test discussion with a suitably trained health care professional. The testing should also be linked with the opportunity for referral for specialist assessment. The discussion should enable the individual to understand the implications of the test, make an informed decision about taking the test, provide a better understanding about the likely routes of transmission and the nature of the disease. C Change, an umbrella group including representatives from the British Liver Trust, hepatitis C patients, consultants and hepatitis specialist nurses has recently produced useful guidance.[56] Recommended areas to be covered in the discussion are included in Appendix 3.

The General Medical Council guidance 'Serious Communicable Diseases'[57] states that consent must be sought before testing for any serious communicable disease, including hepatitis C, except in certain specified and rare circumstances. Consent should only be given after receipt of appropriate information about the implications of the test and the patient must have time to consider and discuss the implications. 'It is the responsibility of the doctor treating the patient to obtain consent to testing for diagnostic purposes'. Those working in laboratories 'may test blood or other specimens for serious communicable diseases only for the purposes for which the samples have been obtained, or for closely related purposes which are in the direct interest of the patient.'[57]

Professionals providing HCV testing should have the knowledge, skills and time to counsel their patients or refer them to a specialist counselling service e.g. at Departments of Genito-Urinary Medicine.

7.4 Support

Many clients diagnosed with HCV infection in future are likely to be drug users with complex psychological, emotional and social problems. They and their families will need support immediately following diagnosis or when problems occur. This support could be provided by a specialist nurse based at a specialist unit, although, at present in Glasgow approximately 50% of HCV antibody positive patients fail to attend for medical assessment.

Data from the counselling clinic at the Brownlee Centre in Glasgow show that many clients who attended the clinic had received their HCV antibody result without having received information or support before or after the test. Many of these clients experienced anxiety for an extended period of time and had grave concerns about their prognosis, anticipated poor quality of life and fears about transmitting the virus through social contact and to family members, partners and children in particular. Similar findings are reported by the Haemophilia Society in two recent reports.[58,59]

Support in the community can be provided by the members of the Primary Care Team but if their knowledge of hepatitis C is limited this may be inadequate and some clients may not be registered with a GP. Support is also available from drug services provided by NHS and non-statutory organisations. Professionals within these organisations should be appropriately trained so that they can offer additional support to clients with HCV infection. Valuable support and information is provided by national and local patient organisations.

7.5 Should high-risk groups be screened for hepatitis C?

Screening is a form of secondary prevention and 'seeks to identify an unsuspected disease or pre-disease condition for which an effective intervention is available.'[60] It has been suggested that targeted screening should be introduced for the asymptomatic population at high risk of acquiring HCV.[61] No new population screening programmes should be introduced without a recommendation from the National Screening Committee (NSC).

Screening high risk populations at present does not fulfil the NSC screening criteria for the following reasons:

- there is no good evidence yet that treatment in mild disease is beneficial
- management of patients should be optimised first
- the infrastructures should be in place to manage patients already diagnosed plus any new cases identified from screening
- benefit from treatment must outweigh physical and psychological harm
- the availability of combination therapy is not guaranteed

The Wessex Institute modelled the cost effectiveness of screening Genito-Urinary Medicine clinic attendees and intravenous drug users. They concluded that 'the evidence of the benefits, harms and costs of a screening programme in either population is inadequate' and that 'great uncertainty surrounds the overall value of screening asymptomatic individuals in the populations considered.'[62] This analysis will need to be revised in the light of improved response to combination therapy.

Systematic population screening of high risk groups is not justified at present but counselling with the opportunity for testing should be offered to people in high risk groups as an integral part of discussion on the management of their risky behaviour.

8. MANAGEMENT OF PATIENTS WITH HEPATITIS C

The management of patients with hepatitis C includes their care from diagnosis through to palliative care for end stage liver disease and should form a seamless integrated pathway of care. Care of patients with hepatitis C can involve a wide range of professionals in the NHS but also in prisons and the voluntary sector, (as described in section 5). Communication and collaboration between these professional groups and co-ordination of services are essential for delivery of good quality care. Patients who are newly diagnosed with hepatitis C need support, accurate and consistent advice and information.

8.1 How should patients be managed?

All new patients who are found to be HCV antibody positive should be offered the opportunity of referral to a specialist clinic. A Consultant Hepatologist, Gastroenterologist or a Consultant in Infectious Diseases should lead this clinic. The patients who acquired their HCV from blood transfusions will have been identified following the lookback exercise in 1995. Most patients with haematological conditions will remain under the care of a haematologist but there should be close collaboration with a hepatologist, and also an infectious diseases specialist if the patient also has HIV. It must be emphasised that the management of patients with hepatitis C involves more than just the provision of antiviral therapy. See Figure 4 below for management pathway.

8.2 Specialist advice and information

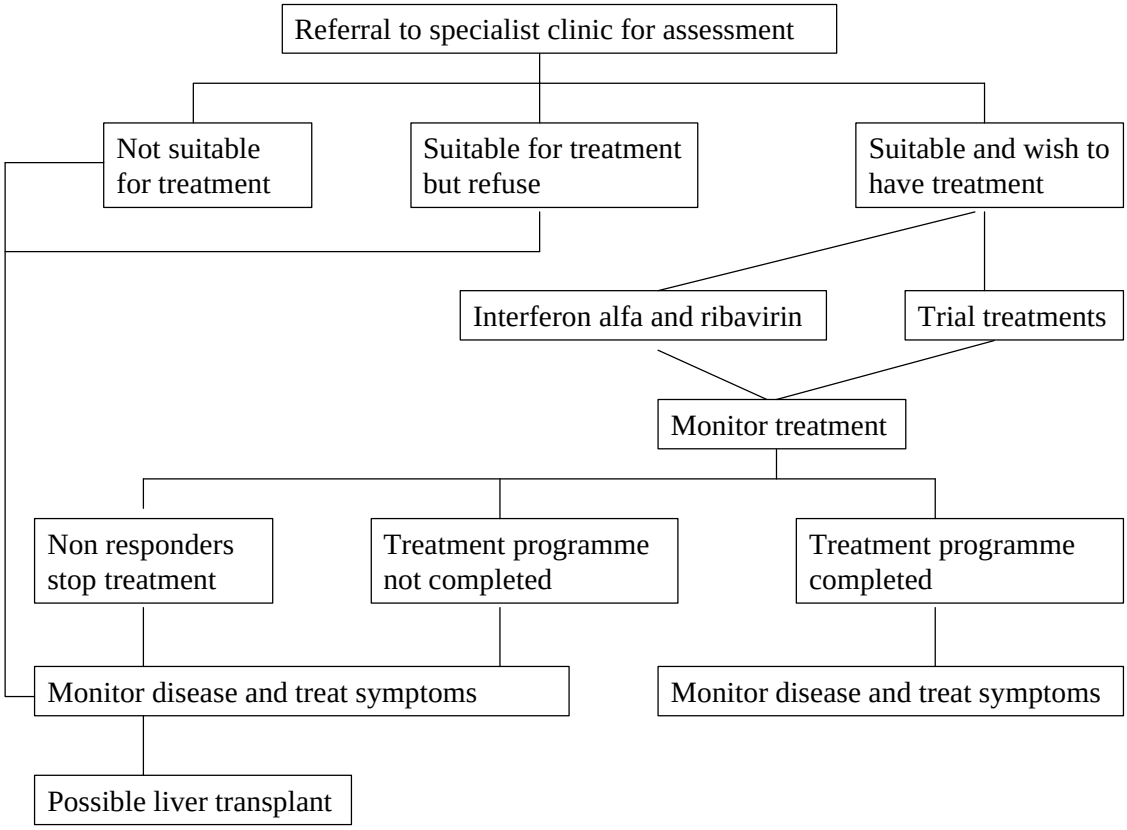
Patients should have received counselling before and after their HCV test but many patients will be anxious about their condition and require considerable explanation and reassurance. The time from diagnosis to receiving specialist advice should be short. An explanation of the nature of the infection, the potential sources of infection and the natural history of the illness as far as is known will be required. Patients should be given relevant written information and encouraged to call back with further questions. The Clinical Nurse Specialist can have an important role in providing ongoing information and support. Several visits may be required for each patient. The physician needs to explain what investigations are appropriate, the plan for follow-up and possible treatment options. The importance of avoiding alcohol must be emphasised as this increases the rate of disease progression.

8.3 Investigations

All HCV antibody positive people require assessment on an individual basis. Investigations will involve relevant serological tests, including PCR for HCV-RNA, liver function tests, ultrasound examination of the liver and where appropriate, liver biopsy. Liver biopsy, though often valuable, is not always a pre-requisite for drug treatment, for instance in haemophiliacs.

The British Society of Gastroenterology has recently published ‘Guidelines on the use of liver biopsy in clinical practice’[63] and recommends that patients with chronic hepatitis C who are being considered for antiviral therapy should undergo liver biopsy. Many patients will require liver biopsy during investigation of their liver disease but because of the invasive nature of the investigation this should only be considered if the results will affect their management.

Figure 4. Management pathway for patients with hepatitis C



8.4 Antiviral treatment in chronic hepatitis

The aim of antiviral treatment is to prevent the progression to irreversible liver disease. There are two licensed treatments for hepatitis C – interferon alfa and ribavirin. Ribavirin is not effective on its own and should only be used in combination with interferon alfa. Both drugs have several absolute and relative contraindications and should only be prescribed after specialist assessment.

Treatment is regarded as successful if abnormal liver function tests return to normal and the HCV RNA is undetectable in the serum. A complete response is defined as response at the end of treatment and a sustained response is one that is maintained for at least 6 months after the treatment is stopped. Patients with a sustained response are thought unlikely to develop cirrhosis and liver failure. It is acknowledged that these outcomes are surrogate markers and it is still unclear whether a sustained response improves the long term prognosis or if a sustained response equates to a cure.

Until 1999 interferon alfa monotherapy was the only treatment option. Three million units of interferon three times a week for 12 months produced a sustained biochemical response in 30% of patients.[64] Higher doses and longer duration of treatment increases the response rate but this must be balanced against the increased risk of side effects.[64,65] Treatment was stopped in those who did not respond within three months.

Combination therapy with interferon alfa and ribavirin was licensed in 1999. There is now good evidence that combination therapy is significantly more effective than interferon alone in patients not previously treated with interferon.[66-68] In a well designed randomised controlled trial that compared twelve months interferon plus placebo to six

and twelve months interferon plus ribavirin, 19%, 35% and 43% of patients, respectively, sustained a virological response.[66] In patients who have been treated with interferon and relapsed, re-treatment for six months with combination therapy is more effective than re-treatment for six months with interferon alone.[69] The sustained response rate in the combination group was 49% compared to 5% in the interferon plus placebo group.[68,69] The results of these studies must be compared cautiously with earlier ones as the outcomes used have changed over time i.e. from biochemical (reduction in serum ALTs) to virological outcomes (loss of viral RNA).

HCV PCR positive individuals who are considered suitable and wish to have treatment should have combination therapy with interferon and ribavirin for six to twelve months.

8.5 What factors influence the decision to treat/not to treat/defer treatment?

Contra-indications to treatment with combination therapy include:

- patients who are unwilling or unable to comply with therapy
- on-going injecting drug use
- patients with significant co-morbidity due to neoplasia or cardiac, respiratory, or renal disease
- pregnancy, breast feeding or risk of pregnancy during treatment
- male partners of women not using contraception
- active alcohol abuse
- patients with evidence of another cause for chronic hepatitis, especially auto immune liver disease
- history of epilepsy
- history of severe mental illness
- specific contra-indications or sensitivity to either drug.

8.5.1 Predictors of a poor response to antiviral treatment

- decompensated cirrhosis i.e. liver failure
- advanced HIV disease

8.5.2 Liver biopsy findings

In patients with minimal or mild inflammation with no fibrosis treatment can be deferred pending the future development of improved drug treatments. Such patients may be offered a further biopsy every 3-5 years to monitor progression and reassess indications for treatment. There is no evidence yet for the benefit of treating patients with mild disease. However there may be certain circumstances where patients may benefit from treatment of mild disease e.g. if planning a pregnancy and they request treatment prior to conception. Patients with mild disease are currently being recruited for a MRC multi-centre clinical trial.

8.6 Treatment options[17,66,67,69]

- In patients with infection with genotype 1 and baseline viral load of more than 2 million copies/ml twelve months treatment with interferon and ribavirin is recommended.
- In those with advanced disease i.e. bridging fibrosis or cirrhosis, treatment for twelve months with combination therapy is recommended, irrespective of genotype.
- In all other patients, irrespective of genotype, and those who have previously failed to respond or relapsed after interferon monotherapy six months combination therapy is appropriate.

8.7 Monitoring during treatment

During drug treatment, patients should be monitored at one, two and four weeks, then monthly thereafter. Full blood count, liver function tests, urea and electrolytes, and thyroid function tests should be checked. HCV PCR should be checked at 6 months, on completion of therapy, and at 6 months post treatment. Patients should be monitored annually thereafter.

8.8 Non drug treatment

In those in whom antiviral treatment is not considered appropriate, on-going counselling, monitoring of liver disease and screening for the complications of liver disease are important. The timing of clinic visits will depend on the individual patient's needs. Most asymptomatic patients with early liver disease can be reviewed annually and liver function tests monitored. PCR for HCV-RNA will not usually be necessary and should not be repeated unless therapy is being considered.

8.9 Cirrhosis

Patients with cirrhosis are at risk of developing gastro-oesophageal varices and hepatocellular carcinoma. While there are no data to recommend screening for all patients, it is accepted that those with cirrhosis should have four to six monthly serum alpha-fetoprotein and ultrasound. Patients with hepatocellular carcinoma less than 5cm, detected by ultrasound, or with a steadily rising alpha-fetoprotein should be considered for liver transplantation. Also, in those with cirrhosis, endoscopy should be carried out every two years to check for varices (annually if small varices are evident). In patients suffering from medium or large varices, prophylactic therapy with propanolol or endoscopic variceal band ligation should be initiated, as appropriate. Patients with decompensated liver disease (i.e. ascites or encephalopathy) should be considered for transplantation.

Hepatitis C is now the commonest indication for transplant in most centres in England. Prior to 1995 no transplants had been carried out for hepatitis C in Scotland but since then there have been 2-3 a year. It is estimated that this could increase to 10 – 20 per year in the next few years.

8.10 Special groups

8.10.1 Pregnant women

Counselling and support are vitally important in pregnant women infected with HCV. Drug treatment with ribavirin is contra-indicated because of its teratogenic effects and should only be used in patients using effective contraception. Pregnancy should be avoided for a further six months after stopping treatment. The risk of vertical transmission to baby is low, at around less than 5% and there is little evidence to suggest the best method of delivery or to suggest mothers should not breast feed.

8.10.2 Children born to mothers who are HCV antibody positive

Antibodies cross the placental barrier, therefore babies born to mothers who are HCV antibody positive will also be HCV antibody positive. Antibody testing should be deferred until after the baby is 12 months old. All children testing positive should be referred to a paediatrician for assessment and follow up.

8.10.3 Prisoners

Those committed to custody who are already attending a specialist clinic should be permitted to continue to attend such a clinic. Prisoners newly diagnosed as suffering from HCV infection should be offered the opportunity of referral to an appropriate

specialist clinic. Health Boards and prisons locally have joint responsibility in planning for the delivery of services to HCV positive prisoners, in order to ensure that this group is not disadvantaged on account of being in custody. The Scottish Prison Service are responsible for provision and funding of primary care for prisoners but are not responsible for costs of secondary care.

8.11 Complementary therapies

Many hepatitis C individuals are exploring the potential benefit of complementary therapies including Chinese medicine, and report some symptomatic relief. Small studies are underway in Australia and the UK and some have shown an anti-inflammatory effect in chronic liver disease. At present there is no good evidence for the effectiveness or safety of complementary therapies. Large, well-designed studies with appropriate baseline data and outcome measures are needed to evaluate the effectiveness of Chinese and other traditional medicines in the management of hepatitis C.

8.12 Current situation

A brief questionnaire was distributed to consultants in gastroenterology, hepatology and infectious diseases to estimate how many patients are being actively followed up and how many are receiving treatment. Approximately 1000 are attending Infectious Disease Units, about 500 of these are in Glasgow, of whom 85% are IDUs and about 10% have, thus far, received antiviral treatment. A further 1100 are under active follow up by the gastroenterologists or hepatologists in Edinburgh and Glasgow.

At 31st December 1999 there were 551 Patients on the Royal Infirmary of Edinburgh (RIE) database. The database includes patients who have been assessed and had a liver biopsy. 66% of the patients were male and 64% reported injecting drug use as a risk factor. The database does not include patients with haemophilia unless they have had a biopsy. 203 of these patients have received treatment, 100 with interferon and 103 with interferon plus ribavirin. So far 31/166 sustained a response to treatment, 25% with interferon plus ribavirin and 9% with interferon alone. 35 patients are currently waiting to start treatment. Therefore in Edinburgh, 43% of patients investigated were eligible and agreed to treatment. Other centres will have different proportions of patients suitable and willing to accept treatment and this may range from 10-40%. This proportion is likely to increase as disease progression occurs and treatment options improve. Health Boards will need an accurate estimate of the local demand for ant-viral treatment from their clinical colleagues to estimate likely costs of funding antiviral drugs.

8.13 Hospital activity data

Most hospital activity for hepatitis C is in the outpatient setting at present but some limited information is available from the SMR01 data (discharges from non-obstetric/non-psychiatric NHS hospitals in Scotland). ICD 9 (International Classification of Diseases) had an inclusive code for viral hepatitis but ICD10 classifies hepatitis C separately as acute (B17.1) and chronic (B18.2).

Since April 1996 there have been 1031 episodes for hepatitis C in Scotland for 1996/97 and 1296 for 1997/98 and 1452 for 1998/99. A substantial number of these are classified as acute hepatitis, which is surprising because only a very small proportion of cases present as acute hepatitis. Some of these episodes will probably be misclassification of chronic hepatitis as acute, as some acute cases have an additional diagnosis of cirrhosis or ascites, which is clearly inappropriate

The SMR01 data is presented by Health Board in Appendix 4. The tables in Appendix 4 show all episodes of hepatitis C, and also the number of episodes with cirrhosis, ascites, variceal bleeds, hepatic encephalitis and hepatocellular carcinoma. The number of liver biopsies is also given by Health Board.

9. RESOURCE IMPLICATIONS

9.1 Costs of primary prevention and health promotion

This report emphasises the importance of primary prevention of hepatitis C. Effective primary prevention and health promotion will need to be adequately resourced and must not be to the detriment of existing prevention strategies for other bloodborne pathogens.

9.2 Costs of investigation, treatment and monitoring

These will include

- Initial counselling and testing
- Evaluation of new patients
- Further assessment if considered for treatment, including liver biopsy
- Monitoring during treatment
- Surveillance after treatment
- Follow up of those not treated
- Surveillance of patients with cirrhosis will include regular alfa feto-protein and ultrasound, plus endoscopy every 1-2 years.

Costs vary across Scotland and each Health Board will need to ensure that the resource implications of investigation, monitoring and surveillance are included and be aware that estimating the drug costs alone is insufficient. There will also be a considerable number of patients referred and assessed who do not receive antiviral treatment and who will still need investigated and monitored.

9.3 Costs of virological investigation

There was insufficient information available to reliably cost the use of ELISA plus PCR in place of the normal practice of ELISA, RIBA and then PCR if necessary. The resource implications will vary in each Health Board area especially where local laboratories may wish to develop PCR testing instead of continuing to send samples to the Regional Virus Laboratories. The funding of all virological tests for HCV requires clarification.

9.4 Costs of interferon alfa and ribavirin

The NHS list price of interferon alfa at 3 million units three times a week (3MU TIW) is £2,652 for 12 months. The cost of interferon (3MU TIW) plus ribavirin (1000-1200mg per day) for six months is £4,537 -£5,180 and twelve months is £9,074 -£10,361. The dose of ribavirin is determined by body weight

9.5 Costs of caring for patients with liver failure and hepatocellular carcinoma

Up to 70% of costs of caring for someone with hepatitis C are incurred during the late stages of the disease in those with complications of liver failure i.e. ascites, oesophageal varices and hepatic encephalopathy. This will include regular endoscopy and band ligation of varices.

9.6 Costs of liver transplants

Cost of surgery, plus drugs after transplant, is £46,551. (National contract cost)

9.7 Cost effectiveness of antiviral treatment

Although SNAP reports do not normally consider cost effectiveness in detail, it has been included in this report as two members of the working group have undertaken considerable work in this area. The National Institute of Clinical Excellence in England is currently reviewing combination therapy but the report is not yet available.

In 1998 the Scottish Health Purchasing Information Centre (SHPIC) produced a report on the costs and benefits of drug treatment for hepatitis C.[65] This report was updated in 1999[68] but the true cost of ribavirin was not available at that time.

The analysis was based on a spreadsheet model of an imaginary cohort of 1000 individuals progressing through the various stages of chronic hepatitis C infection. A number of clinical and economic assumptions had to be made because of the nature of the disease. The model attempts to predict the natural history of the disease, to identify distinct health states through which a cohort of patients pass, the time they spend in each state, the NHS costs of treating a patient in each state and the health consequences of being in that state. The options considered were: do nothing except treat symptomatically; treat with interferon alfa for three months and treat responders for a further nine months; and treat with combined interferon plus ribavirin for six months (combination therapy). The conclusion was that under conventional cost-effectiveness criteria, combination therapy was probably the most cost-effective treatment option but this analysis was severely limited by using 1995 costs of ribavirin.

For the SNAP report the SHPIC model has been reviewed and updated:

- the assumptions used have been reviewed in the light of recently published comparable models
- the NHS cost of ribavirin is included
- the cost data have been updated
- the response rates used are virological response rates from the recent RCTs[66,67,70]
- all patients received 12 months interferon alfa i.e. it was not assumed that patients stopped after 3 months. This reflected the comparison in the RCTs.
- the definition of health gain is changed from extending life alone to gains in quality-adjusted life-years (QALYs).
- two other options for combination therapy are considered – extending first-line therapy to 12 months and treating relapsers after treatment with interferon alone.

The recently published models[70-74] have been used to assess how others had modelled the natural history of hepatitis C. Each of the SHPIC assumptions about the natural history were reviewed and found to be robust. The only change to the clinical assumptions made to the model were a slightly slower rate of progression from chronic hepatitis C to cirrhosis, and cirrhosis to hepatocellular carcinoma. There has been little change to cost assumptions apart from drug costs. Cost per Quality Adjusted Life Year(QALY) has been incorporated in place of cost per life year saved using the utility values from the literature.[71-73] This reflects the fact that benefits of drug treatment include non-fatal illness averted as well as survival gains.

A more detailed health economics report is included as Appendix 5.

The SHPIC model was rerun using the changes described above and the results are summarised below. To determine if the additional costs of treatment are worthwhile it is necessary to perform a marginal analysis i.e. to assess the additional costs and benefits associated with moving from one treatment option to another.

- In those patients not previously treated with interferon, the *additional* cost per QALY gained from treatment with interferon plus ribavirin (combination therapy) for 6 months compared to interferon monotherapy for 12 months was £7,274.

- In those patients not previously treated with interferon, the *additional* cost per QALY gained from treatment with combination therapy for 12 months compared to combination therapy for 6 months was £36,650. (See below for further analysis).

- In patients who relapsed after treatment with interferon, the *additional* cost per QALY gained from treatment with combination therapy for 6 months compared to no active treatment was £3,657.

The decision about duration of treatment i.e. 6 or 12 months combination therapy, is determined by a range of clinical indicators of i.e. genotype, viral load, age, level of fibrosis and sex but it was not possible to incorporate this level of detail into the model. The response rates used in the model were overall response rates from the RCTs and this should be taken into account when considering the difference in cost per QALY between 6 and 12 months combination therapy. In sub-group analysis those patients with several independent indicators of good response gain negligible benefit from the longer course of treatment of combination therapy at double the cost (54% vs. 56% sustained response), whereas those with fewer indicators of a good response the costs are double but so are the benefits (14% vs. 30% sustained response).[66]

A simple sub group analysis was undertaken using the sustained responses from the RCT[66] and this substantially revises the additional cost per QALY gained. However such an analysis required that all the clinical variables in the model apply equally to the selected sub group of patients and the numbers in the sub groups in the clinical trials are relatively small so the results should be treated with caution. If these caveats are accepted then the results from the sub group analysis are shown below.

- In those patients not previously treated with interferon and with three or more indicators of a good response, the *additional* cost per QALY gained from treatment with combination therapy for 6 months compared to interferon monotherapy for 12 months was £5,545.

- In those patients those patients not previously treated with interferon and with three or more indicators of a good response, the *additional* cost per QALY gained from treatment with combination therapy for 12 months compared to combination therapy for 6 months was £150,716 and is clearly unacceptable.

- In those patients not previously treated with interferon, with two or less predictors of a good response, the *additional* cost per QALY gained from treatment with combination therapy for 6 months compared to interferon monotherapy for 12 months was £18,389.

- In those patients not previously treated with interferon, with two or less predictors of a good response, the *additional* cost per QALY gained from treatment with combination therapy for 12 months compared to combination therapy for 6 months was £17,640.

These results can be interpreted in several ways. A possible 'rule-of-thumb' is that services up to £10,000 per QALY represent 'good value', services between £10,000 and £20,000 are 'acceptable', between £20,000 and £30,000 cost-effectiveness appears more doubtful, and above this cost-effectiveness is poor. The rationale for these bandings is as follows:

- There are many common health services that have a cost per QALY below £10,000. These include hip replacements, the statins to lower cholesterol in patients with heart disease, and breast cancer screening. It is, therefore, assumed that new services achieving a comparable level of cost-effectiveness would be funded.

- Services in the range of £10,000 to £20,000 are usually funded but are perceived to be somewhat expensive. Examples include a range of drugs for cancer chemotherapy, drug treatment of mild and moderate hypertension, coronary artery bypass grafting for mild to moderate angina.

- Services in the range £20,000 to £30,000 per QALY are not funded by some health boards – examples include donepezil and taxol for ovarian cancer.

- Services over £30,000 per QALY are at the forefront of the rationing debate in the NHS – examples include beta interferon for multiple sclerosis and cancer drugs that extend survival by one or two months.

It is worth emphasising again that these cost per QALYs should only be used to assist decision making and they should not be adhered to rigidly. In particular, the level of funding for new services such as this varies from year-to-year. In a year when more money is available, Health Boards could afford to purchase things with a higher cost per QALY. On the other hand, when money is especially short the cost-effective threshold might be much lower.

On cost-effectiveness grounds, therefore, the priority for any money targeted on this group would be to offer combination therapy to previous relapsers. The second priority would be to offer combination therapy for six months to those patients who had not previously received interferon. The final stage would be to offer one year of combination therapy to those who had not previously received interferon. The marginal cost per QALY for this last group appears quite high but would be improved by targeting those patients most likely to benefit. For completeness these figures should also be compared to other ways of improving the health of this group: for example, needle exchanges may prevent the spread of HCV in the first place. While this would not help people who already have the disease, Health Boards may take a population view on this matter and consider that preventative strategies are better value than the least cost-effective drug treatments described above.

9.8 Cost effectiveness of needle and syringe exchanges

Potentially, needle exchanges have many benefits that might justify their funding. Concentrating on one aspect thus gives a misleading impression of their overall impact. However, if the scheme can be justified on the basis of this single aspect alone then any other benefits can be seen as a bonus, reassuring decision-makers that the conclusions reached are robust.

9.8.1 The annual cost of needle exchanges

Accessing the cost data for needle exchanges proved less than straightforward. However, Greater Glasgow Health Board holds data on schemes run through pharmacies so this has been used to illustrate the approach. In the period 1st April to 30th September 1999, the cost of this scheme was £63,532 in fees plus £51,250 on equipment. The total cost is thus £114,782. There were 26,707 client contacts, with 186,198 syringes issued and 149,218 returned.

9.8.2 The lifetime costs of a case of hepatitis C

The approach used has been described in section 9.7 on the economics of drug treatment. A model of the disease history, including different health states, was constructed. Data from previously published studies was used to estimate how a cohort of patients moved through those states over time. NHS treatment costs were estimated for each state and health consequences were estimated as life-years lost. In line with standard economic practice, costs and benefits occurring in future years were discounted at 6% per annum to give a present value.

Assuming the typical individual newly diagnosed is 30 years old and has a life expectancy of 30 years, the results are as follows:

- the lifetime cost of hepatitis C per individual is £4,601, discounted to present value of £2,019
- loss of life expectancy is 2 life-years, discounted to present value of 1 life-year.

9.8.3 'Threshold' level of effectiveness

From the two pieces of data above, we can estimate how many cases of hepatitis C the exchanges must prevent each year in order to reach different levels of cost-effectiveness. The very strictest criterion would be to use discounted lifetime costs of the disease and require that the scheme release resources that equal the value of the costs (sometimes referred to – inaccurately – as 'paying for itself'). Under this extreme condition, the total cost of the exchanges at £114,782 would be compared to the discounted lifetime cost of £2,019 with no account taken of health gain. The number of cases that the exchange would have to prevent would be 57 (£114,782/£2,019 = 57) Given the number of client contacts, a case would have to be prevented per 468 client contacts (26,707/57 = 468).

The 'pay for themselves' condition is not applied to other areas where the NHS is willing to pay to achieve health gains and it is harsh to apply this condition to needle and syringe exchanges schemes. Supposing that the NHS was willing to pay up to £10,000 for one year of life saved. Given the costs of needle exchanges, the discounted lifetime costs and discounted survival, the number of cases that would have to be prevented to achieve a cost-effectiveness ratio of £10,000 per life-year saved would be between 9 and 10 cases. A case would have to be prevented every 2,811 client contacts.

It is worth emphasising again that this assumes that the only benefit of needle exchanges is the prevention of HCV transmission. In practice the transmission of a variety of other blood-borne viruses (including HIV) will also be reduced if the scheme operates as intended. However, if needles and syringe exchanges can be justified by their impact on hepatitis C alone, even with the speculative method employed, then the case is much more robust once the other benefits are considered.

It was not possible to take this forward within the time constraints of the report but is obviously an area that merits further consideration.

10. CHANGES TO SERVICE PROVISION TO MEET NEED

What should patients expect from an ideal service?

- An integrated pathway of care from the patient's perspective.
- HCV antibody testing with pre and post test discussion provided in a suitable setting by appropriately trained professionals.
- Access to accurate and easy to understand information, advice and support for patients and their families.
- Co-ordinated services to ensure good communication, collaboration and consistency of approach.
- Opportunity for rapid referral to specialist service for assessment of liver disease as variability of progression, and poor correlation of symptoms and liver function tests with severity of fibrosis makes management in primary care difficult.
- Referral centre should be adequately resourced with access to virology and pathology.
- Management should not be influenced by route of acquisition.
- Access to the most clinically and cost effective treatment.
- Access to clinical nurse specialist to provide ongoing information, advice and support plus assistance with management including antiviral treatment.

What is described above is an ideal service for patients with hepatitis C but each Health Board clearly has markedly different needs, as shown by the prevalence of known infection, and will also have different levels of service already in place. Health Boards will have to take their particular characteristics into consideration when identifying the priorities for development in their area. Few areas have the capacity to provide this level of service without significant investment that will need to be prioritised against other competing demands. An incremental approach over several years will be necessary based on changes that will maximise health gain for their population.

The potential for health gain is considerable by preventing acquisition of the virus by appropriate and comprehensive health promotion and primary prevention initiatives. Individuals can benefit from timely and accurate advice and information from before diagnosis. Ideally *all* patients diagnosed with hepatitis C should be assessed and a decision made whether to consider treatment, defer treatment, or monitor for early detection of cirrhosis and HCC. The aim of treatment is to prevent the progression of disease and patients benefit by avoiding the consequences of irreversible liver disease. It is not yet known if a sustained response equates to a cure and this will require long term cohort studies. The major costs to the health service are incurred by patients with complications of decompensated cirrhosis.

The majority of patients newly diagnosed with hepatitis C are likely to have a history of injecting drug use. Patients who are still injecting are not suitable for treatment because of poor compliance with a difficult treatment given by injection, risk of re-infection and possible morbidity and mortality from drug related causes. They can still benefit from information about the disease, it's likely impact, support and advice. Advice and information on the prevention of transmission can be beneficial to their friends and families.

Hepatitis C is a rapidly changing field and there is likely to be increased demand for counselling, testing, referral, treatment and management of sequelae of liver disease. Treatment options will also be changing rapidly. The priorities for now are effective prevention of new cases, specialist assessment and access to effective treatment for those with the disease.

11. SURVEILLANCE, EVALUATION AND MONITORING

There needs to be continued surveillance of hepatitis C to determine trends in the incidence and prevalence of the disease. Information is required to estimate the burden of disease in Scotland to facilitate the strategic planning of services to meet need. Surveillance should include information on risk factors and routes of transmission. Much of this will be provided by the hepatitis C register held at SCIEH in association with the principal HCV testing laboratories across Scotland. SCIEH and ISD are currently planning a collaborative project linking the hepatitis C register with the SMR01 (hospital discharge records), SMR06 (cancer registration data) and the General Register Office of Scotland death records. This anonymised linked dataset will enable a better understanding of the morbidity, mortality and the risk of HCC associated with hepatitis C

The effectiveness of prevention activities, detection and management of patients including clinical and cost effectiveness of treatment should be monitored and evaluated. A database of patients diagnosed, with outcome data would assist in addressing some of the uncertainties surrounding many aspects of hepatitis C including the natural history, progression and optimal management. The Royal Infirmary of Edinburgh (RIE) has a comprehensive clinical database on the cohort of patients with hepatitis C attending RIE but there would be significant resource implications if this were extended nationally. A UK wide database of patients treated with interferon and ribavirin is being established by the RIE in collaboration with a unit in Southampton.

There are two professional groups in Scotland with a particular interest in hepatitis C - the Scottish Liver Group, hepatologists with responsibility for delivering liver services across Scotland, and the Scottish Viral Hepatitis group which comprises specialists from a wide range of disciplines with an interest in viral hepatitis.

12. RESEARCH NEEDS

- Epidemiology of hepatitis C and disease progression in different sub populations
- The reasons for injecting drug users continuing to share and methods to minimise.
- Benefits of providing other injecting equipment e.g. spoons
- Cost effectiveness of needle and syringe exchange schemes.
- The effect of HCV antibody testing on behaviour, lifestyle and risk of transmission.
- Additional outcomes in randomised controlled trials e.g. quality of life, progression and costs.
- New treatment options to improve sustained response e.g. pegylated interferon with or without ribavirin and triple therapy
- Clarification of the optimal time to commence drug treatment
- Treatment of chronic hepatitis C in the young, old, patients with co-morbidity, those co-infected with HIV, injecting drug users, those on methadone and those with alcohol dependency.
- Benefits of complementary therapies in the management of hepatitis C
- Extended role of the specialist nurse e.g. providing outreach to drugs agencies or drop in clinics especially for those who are marginalised and not in contact with normal services.
- Vaccines

13. CONCLUSIONS

Hepatitis C is a major public health problem affecting approximately 35,000 of Scotland's population. Only about 10,000 individuals are diagnosed and less than 3000 are under active follow up. Injecting drug users are the group most at risk as the virus is not easily spread amongst the general population. Injecting drug use can range from a single incident to regular usage and can affect all strata of society. However, it must be emphasised that hepatitis C is not restricted to past and present injecting drug users and it affects many other groups within our population, including haemophiliacs. Sexual transmission may become commoner route of transmission if the prevalence of infection increases.

Hepatitis C positive individuals should receive an equitable provision of good quality care from diagnosis onwards, which is not influenced by the route of acquisition. The resource implications for the health service are considerable and include the provision of HCV antibody testing on request with pre and post test discussion, investigation and assessment of patients confirmed to have the disease, provision of treatment with interferon and ribavirin, and regular monitoring after treatment. Those not suitable for treatment will need surveillance to detect hepatocellular carcinoma. Some will require treatment for cirrhosis, oesophageal varices and liver failure; this might necessitate liver transplantation.

There is no national strategy to provide guidance on prevention, detection and management. There is currently inequity across Scotland in provision of testing, specialist assessment and access to the most effective treatment.

Hepatitis C can be prevented and it is essential that health promotion and primary prevention measures are in place and co-ordinated with existing drugs strategy and prevention strategies for other bloodborne viruses.

14. RECOMMENDATIONS

Primary prevention

4. A national workshop should be held on the prevention of transmission of hepatitis C amongst injecting drug users in Scotland, sponsored by SNAP and/or the Scottish Executive and involving SCIEH, HEBS, Health Promotion Officers, Scottish Drugs Forum and Scottish Advisory Committee on Drug Misuse. The workshop should review the current preventive measures for hepatitis C in injecting drug users and also identify the most appropriate way to raise awareness of infective risks associated with drug misuse.

Action SCIEH, SNAP and Scottish Executive

5. Recommendations of this national workshop for the primary prevention of hepatitis C should be adequately resourced. This should not be at the expense of existing prevention activities for other bloodborne pathogens.

Action Scottish Executive

6. As a matter of urgency all Health Boards should review their current health promotion and primary prevention activity for all bloodborne pathogens pending the outcome of the national workshop. Primary prevention strategies for bloodborne pathogens must be consistent with the drugs strategies.

Action Health Boards

4. The focus of primary prevention of hepatitis C should be in the drug using population and should include clear and accurate messages about risks of injecting and sharing. Sharing of injecting equipment must be minimised – the aim is reduction to zero.

Action Health Boards and Drug Action Teams

5. Enhanced needle and syringe exchange schemes with health promotion and primary prevention advice should be considered and adequately resourced. These must be easily accessible and consideration should be given to times of opening, geographical spread and outreach services to target groups early in their drug injecting career.

Action Health Boards and Drug Action Teams

7. Health care professionals should receive education and training about hepatitis C, its natural history, prevention and infection control, investigation and management, appropriate to their needs.

   Similar education and training should be offered to other occupational groups within the public, private and voluntary sector who work with drug users.

Action Health Boards, Drug Action Teams and Trusts, plus agencies in the statutory and voluntary sectors

7. Primary prevention must also address other routes of transmission and should include maintaining the optimum screening and treatment procedures for blood and other donations, reducing the risk of sexual transmission, and minimising nosocomial and occupational transmission.

Action Scottish Blood Transfusion Service, Health Boards and Acute Trusts

8. Consideration should be given to the licensing or regulation of body piercing premises to minimise risks of transmission of infection including hepatitis C.

Action Scottish Executive

Detection and Diagnosis

9. All high risk groups should be offered counselling, and testing for hepatitis C if appropriate after discussion. Testing for hepatitis C must include the provision of pre and post test discussion by trained individuals in appropriate settings.

Action Health Boards and Acute and Primary Care Trusts

16. The availability and funding of virological investigations for HCV across Scotland should be clarified and adequate resources made available. As yet there are insufficient numbers of HCV antibody positive patients outside the central belt to justify the introduction of HCV PCR testing at other sites, unless the technology can be extended to other diagnostic work.

Action Scottish Executive and Virology laboratories

17. 'Viral hepatitis' is a notifiable disease and the notification system should be revised to differentiate between different hepatitis viruses.

Action Scottish Executive

18. Virology laboratories should report all new cases of hepatitis C to their local Department of Public Health.

Action Virology laboratories

19. Electronic links should be developed between virology laboratories and Departments of Public Health to facilitate transfer of hepatitis C data.

Action Health Boards and SCIEH

Management

20. Each Health Board should have a local policy for detection, referral and management of patients with hepatitis C and must address the significant resource implications associated with providing a service to care for patients with hepatitis C.

Action Health Board and Trusts

21. A lead clinician or clinicians should develop, deliver and co-ordinate appropriate local services to ensure an integrated pathway of care for all patients with hepatitis C, from diagnosis to endstage liver disease. This could be facilitated by the appointment of clinical nurse specialists.

Action Health Board and Acute Trusts

16. All newly diagnosed patients should be offered referral to a specialist and should have access to specialist counselling and advice.

Action Health Board and Primary Care

17. Interferon plus ribavirin is more effective than interferon alone and Health Boards should consider the relative priority of provision of these drugs for their population. The cost effectiveness of the various regimens should be taken into consideration when decisions are made regarding funding of these drugs.

Action Health Boards and Acute Trusts

18. Surveillance programmes for monitoring patients with progressive chronic liver disease for the early detection of hepatocellular carcinoma and oesophageal varices should be established and resourced.

Action Health Boards, Acute Trusts and the Scottish Liver Group

Surveillance and research

21. Epidemiological surveillance must continue to monitor new cases, routes of transmission and changes in prevalence and incidence, disease progression and effect of interventions. An enhanced national register of hepatitis C cases should be established in collaboration with the existing clinical databases so that the natural history of hepatitis C, the impact of treatment and the healthcare resources utilised by infected patients can be monitored.

Action SCIEH, ISD and the Scottish Liver Group

22. Research funds and initiatives should be targeted at hepatitis C and participation in multi-centre trials should be encouraged.

Action Health Boards and Acute Trusts

APPENDIX 1

GROUPS INVITED TO COMMENT

Scottish HCV Group – patient group with representation from across Scotland

Haemophilia Society – Scottish Branch

Scottish Drugs Forum

Chair of the Drug Action Team Chairs

Chair of the Health Promotion Managers

Dr Finlayson, Chair of the Scottish Liver Group

Professor Brunt, Chair of the Scottish Viral Hepatitis Group

Dr Andrew Fraser, Deputy Chief Medical Officer

APPENDIX 2

HEPATITIS C –THE CURRENT SITUATION

1. Introduction

In order to assess the existing arrangements and current services for hepatitis C in Scotland, a survey was carried out among the 15 Health Boards. During August and September 1999 a questionnaire was circulated to the Consultant in Public Health (Communicable Disease & Environmental Health) in the 12 mainland Boards and to the 3 Island Directors of Public Health. Questions covered a range of issues including the information currently available for professionals and patients, existing policies and protocols e.g. for referral or treatment, the services which were in place, preventive measures being taken and any ongoing research. One mainland Board and one island Board did not complete a questionnaire but responses were received from all 13 other areas. In some cases the CPHM had passed the questionnaire to other professionals with more knowledge of the current situation. It is feasible that the information compiled from the questionnaires is incomplete or inaccurate and may not reflect the exact situation within each Board area. However, there was a considerable degree of consistency in the responses obtained and a reasonable assessment of the current position is as follows.

2. Virology data

In 8 of the 13 Board areas the CPHMs (CD/EH) did not routinely receive information about hepatitis C positive patients from the local virology laboratory. Only 2 CPHMs received information directly from the Blood Transfusion Service. 4 respondents relied solely on the SCIEH summary updates for hepatitis C information. Those that did receive data from laboratories either got a copy of the individual laboratory results or copies of the weekly summary report from the laboratory to SCIEH. One respondent was able to obtain total lists of positive patients on request to the lab.

There is clearly a poor information flow between some clinicians, virology and public health departments. This may be specific to hepatitis C but probably more accurately reflects a widespread problem. If the local CPHMs are unaware of individual cases, this prevents them from offering appropriate public health advice to the health care professionals involved. This may result in less targeted secondary prevention measures for patients and their close contacts and inhibits informed planning of local services.

'Viral hepatitis' is a notifiable disease and although this does not discriminate between the different viruses causing hepatitis there is a medical responsibility to notify. It should be noted that there is no framework to facilitate the transfer of information from virology to public health.

The Blood Transfusion Service is a potential source of information on hepatitis C for epidemiological purposes which appears to be relatively untapped. The lack of patient information available to CPHMs may be a factor in explaining why 6 respondents were unable to estimate the percentage of diagnosed hepatitis C patients who were known to specialist services in their area. A range of 10% to 50% was estimated by other respondents.

3. Information leaflets

In those respondents who were aware of specific patient information leaflets, the British Liver Trust materials were the most commonly used and 3 Boards had produced an in-house information leaflet. Five Board areas had voluntary or support groups for people with hepatitis C or their carers, although some of the support groups listed were drugs

related rather than specific to hepatitis C.

4. Local Policies and Protocols

Only 3 Health Board areas had an existing Board wide policy on the management of hepatitis C. Even these existing policies were not comprehensive and focussed primarily on treatment. Only one Board in Scotland had discussed a paper on hepatitis C at their Board Meeting within the previous 12 months. Only one Board had a specific budget for the management of hepatitis C. Three Boards said they had a protocol for use in primary care, 5 had a local referral policy from primary to specialist care, one had a screening protocol which was still in draft, and 4 said they knew of a written agreed policy for treatment of hepatitis C among local clinicians.

There is clearly therefore, a lack of written guidance on hepatitis C for health professionals in the country, presumably a subsequent lack of standardisation of care, and services and local arrangements are developing in an ad hoc fashion without the existence of a national or local planning framework.

5. Services

When blood tests were done to detect hepatitis C, counselling does appear to accompany testing but nothing is known about the quality of that discussion. This is undertaken by a variety of professionals, including HIV Counsellors, Nurse Specialists at GUM Clinics, Hospital Clinicians, Bloodborne Virus Counsellors, specifically trained nurses, and GPs.

Secondary care was provided predominantly by Gastroenterologists but also by Infectious Diseases Physicians and Genito-Urinary Medicine Physicians and in several Boards by a combination of all three. In at least two rural Boards a General Physician with an interest in hepatitis C was regarded as the local specialist. In one Board, all those infected through previous treatment for blood disorders were cared for by the Director of Haemophilia Services.

In 6 Board areas it was reported that there were no clinics and services for hepatitis C patients locally. In the other 7 only one had specific services solely for hepatitis C patients. The others comprised a mixture of existing gastroenterology or infectious disease services.

Ten Boards said they had no clinical liaison nursing staff for hepatitis C, while one Board had two such nurses, plus a full-time counsellor and 2 other Boards had one specialist nurse.

Ten of the 11 mainland Boards who responded said that they did not offer treatment to current intravenous drug users, although one respondent commented that this was left to clinical choice. The two Island Boards were unaware of any intravenous drug users who had hepatitis C and who were seeking treatment. Eight respondents did indicate that that ex-IDUs would be offered treatment in their area.

6. Prevention

The prevention initiatives mentioned were predominantly general in their nature such as a sexual health strategy, harm reduction initiatives, needlestick policies and services for drug users and one mainland Board had just produced a draft strategy for the prevention of all bloodborne viruses. Five respondents mentioned needle exchanges or specific training programmes for health care workers on bloodborne viruses.

7. Research

Only two respondents were aware of ongoing research in their Board area and the same two respondents commented that patients on drug treatment for hepatitis C were involved in ongoing multi-centre drug trials.

8. Summary

There is no national strategic framework for hepatitis C in Scotland. The survey results suggest that services provided for prevention, detection and management of chronic hepatitis C in some health board areas have developed in an ad hoc manner with little strategic planning or identified funding. There is obviously variation across Scotland and several Boards are currently drafting strategies for hepatitis C or bloodborne viruses.

APPENDIX 3

ISSUES FOR DISCUSSION IN PRE AND POST TEST DISCUSSION

Pre test discussion

- Accurate information on hepatitis C infection including routes of transmission and risk reduction, natural history of disease, currently available medical treatments and support.

- The nature of the test and the implications of the result including the issue of the window period and the relevance of an antibody positive result.

- Personal implications of having test

- Identifying issues relevant to the individual which may impact upon their overall health – drug use, homelessness, possible risk of other infections, mental health problems, sexual health problems, other health problems.

- Assessing the psychological coping strategies available to the individual in the event of a positive result.

- Arranging for the individual to obtain the result of the hepatitis C test.

Post-test discussion

- Communicating the result of the test in a clear and direct manner and ensuring that the individual understands the result.

- Reinforcing the implications of the given result.

- Discussing health behaviour – safer sex and safer drug use to reduce the risk of transmission.

- Facilitating access to appropriate medical, psychological or social services as required.

- Offering written information and contacts of local and national support organizations.

For additional information see 'Recommendations for pre and post test consultation procedures for hepatitis C virus in Adults' by C Change[56]

APPENDIX 4
Hospital activity data from the SMR01 database

Table 1. Number of episodes with a diagnosis of hepatitis C (17.1 – acute, B18.2 – chronic) in any position, 1996/7,1997/8 and 1998/9

Area of residence	Acute and Chronic			Acute and Chronic			Acute and Chronic		
	IP	DC	**Total**	IP	DC	**Total**	IP	DC	**Total**
Argyll and Clyde	48	4	**52**	65	9	**74**	55	6	**61**
Ayrshire and Arran	36	16	**52**	62	9	**71**	66	6	**72**
Borders	3	0	**3**	6	0	**6**	14	3	**17**
Dumfries and Galloway	18	2	**20**	25	3	**28**	24	2	**26**
Fife	28	6	**34**	29	12	**41**	55	4	**59**
Forth Valley	48	6	**54**	53	7	**60**	66	12	**78**
Grampian	88	0	**88**	149	6	**155**	152	8	**160**
Greater Glasgow	300	19	**319**	347	53	**400**	403	103	**506**
Highland	20	0	**20**	16	3	**19**	16	3	**19**
Lanarkshire	34	3	**37**	47	8	**55**	86	17	**103**
Lothian	262	8	**270**	280	23	**303**	210	31	**241**
Orkney	0	0	**0**	1	0	**1**	3	0	**3**
Shetland	23	0	**3**	0	0	**0**	2	0	**2**
Tayside	74	3	**77**	58	25	**83**	92	13	**105**
Western Isles	2	0	**2**	0	0	**0**	0	0	**0**
Other/NK	8	0	**8**	1	0	**2**	31	0	**31**
Scotland	**968**	**67**	**1031**	**1138**	**158**	**1296**	**1244**	**208**	**1452**

Source ISD (Scotland), SMR01 (discharges from non-obstetric/non-psychiatric NHS hospitals in Scotland). 1998/99 figures are provisional.

(IP – inpatient, DC – day case)

Table 2. Number of episodes with a diagnosis of hepatitis C (17.1 – acute, B18.2– chronic) and cirrhosis, ascites, variceal bleeds, hepatic encephalitis or hepatocellular carcinoma in any position, 1996/97,1997/98 and 1998/99

Area of residence	Cirrhosis (K74)			Ascites (R18)			Oesophageal Varices (I85)			Hepatic Encephalitis (K72)			Hepatocellular carcinoma (C22.0)		
	96/97	97/98	98/99	96/97	97/98	98/99	96/97	97/98	98/99	96/97	97/98	98/99	96/97	97/98	98/99
Argyll and Clyde	6	9	10	0	0	1	4	5	1	1	5	2	0	0	4
Ayrshire and Arran	4	4	5	1	1	2	0	6	2	0	1	0	0	0	0
Borders	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Dumfries and Galloway	0	0	0	0	0	0	0	0	0	4	0	0	0	0	0
Fife	15	12	6	1	2	3	2	5	0	3	0	4	3	7	0
Forth Valley	11	2	1	0	0	2	0	0	1	0	1	0	3	0	0
Grampian	4	3	3	0	1	4	1	1	4	3	4	5	0	4	2
Greater Glasgow	16	8	13	9	2	5	4	9	8	4	3	7	3	6	2
Highland	0	0	1	0	0	0	0	3	0	1	0	0	0	0	0
Lanarkshire	1	1	3	0	0	2	0	2	9	1	0	1	2	1	9
Lothian	36	32	23	19	4	6	4	8	12	5	1	17	17	4	5
Orkney	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Shetland	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tayside	4	9	4	0	0	0	0	1	1	1	2	3	0	0	0
Western Isles	2	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Other/NK	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Scotland	**100**	**80**	**72**	**31**	**10**	**25**	**16**	**40**	**38**	**23**	**17**	**39**	**28**	**22**	**22**

Source ISD (Scotland), SMR01 (discharges from non-obstetric/non-psychiatric NHS hospitals in Scotland). 1998/99 figures are provisional.

Table 3. Number of episodes with a diagnosis of hepatitis C (17.1 – acute, B18.2 – chronic) with a liver biopsy in 1996/97,1997/98 and 1998/99

	Liver biopsy								
Area of residence	**1996/97**			**1997/98**			**1998/99**		
	IP	DC	**Total**	IP	DC	**Total**	IP	DC	**Total**
Argyll and Clyde	11	1	**12**	24	0	**24**	9	1	**10**
Ayrshire and Arran	14	2	**16**	16	2	**18**	11	0	**11**
Borders	0	0	**0**	2	0	**2**	6	0	**6**
Dumfries and Galloway	7	0	**7**	1	1	**2**	3	0	**3**
Fife	10	0	**10**	3	0	**3**	7	0	**7**
Forth Valley	14	3	**17**	12	5	**17**	12	4	**16**
Grampian	32	0	**32**	37	1	**38**	21	0	**21**
Greater Glasgow	82	1	**83**	102	24	**126**	68	40	**108**
Highland	3	0	**3**	2	0	**2**	2	2	**4**
Lanarkshire	13	0	**13**	24	2	**26**	26	6	**32**
Lothian	62	1	**63**	53	6	**59**	52	7	**59**
Orkney	0	0	**0**	1	0	**1**	1	0	**1**
Shetland	1	0	**1**	0	0	**0**	1	0	**1**
Tayside	14	1	**15**	13	12	**25**	18	7	**25**
Western Isles	0	0	**0**	0	0	**0**	0	0	**0**
Other/NK	0	0	**0**	0	0	**0**	2	0	**0**
Scotland	**263**	**9**	**272**	**290**	**53**	**343**	**237**	**67**	**304**

Source ISD (Scotland), SMR01 (discharges from non-obstetric/non-psychiatric NHS hospitals in Scotland). 1998/99 figures are provisional.

(IP – inpatient, DC – day case)

APPENDIX 5

COST EFFECTIVENESS OF INTERFERON AND RIBAVIRIN

1. Introduction

In 1998 the Scottish Health Purchasing Information Centre (SHPIC) produced a report on the costs and benefits of drug treatment for hepatitis C.[65] This report was updated in 1999[68] but the true cost of ribavirin was not available at that time.

The analysis was based on a spreadsheet model of an imaginary cohort of 1000 individuals progressing through the various stages of chronic hepatitis C infection. A number of clinical and economic assumptions had to be made because of the nature of the disease. The model attempts to predict the natural history of the disease, to identify distinct health states through which a cohort of patients pass, the time they spend in each state, the NHS costs of treating a patient in each state and the health consequences of being in that state. The options considered were: do nothing except treat symptomatically; treat with interferon alfa for three months and treat responders for a further nine months; and treat with combined interferon plus ribavirin for six months (combination therapy). The conclusion was that under conventional cost-effectiveness criteria, combination therapy was probably the most cost-effective treatment option but this analysis was severely limited by using 1995 costs of ribavirin.

Several models have recently been published [70-74] and have been used to review the economic and clinical assumptions used in the SHPIC reports.[65,68]

2. Updating cost data

In the two years since the SHPIC model was published, little has changed in terms of the costs involved except for the substantial increase in ribavirin. The cost of ribavirin used in the original model was £163 and the actual cost is £494 for 1000mg and £593 for 1200mg. An average cost of £543 is used in the model. The costs of interferon alfa are identical in the latest BNF. Minor changes have been made to the costs of general medical out-patient (up to £67 from £57) and in-patient resource use (up to £206 from £204).

3. Virological response rates

The three RCTs reviewed in the SHPIC update[68] used virological response rates and these were used instead of the biochemical response rates used originally. All patients were assumed to receive the full six or twelve months interferon i.e. non responders not stopping after three months as this reflected the true comparison in the clinical trials.

The sustained response rates used in the model were from two clinical trials [66,69] and are as shown in the tables overleaf.

Table 1. Overall virological sustained response rates[66]

Treatment	Duration	Sustained response rate
Interferon alfa plus placebo	48 weeks	19%
Interferon alfa plus ribavirin	24 weeks	35%
Interferon alfa plus ribavirin	48 weeks	43%

Table 2. Sub group analysis – three or more predictors of good response[66]

Treatment	Duration	Sustained response rate
Interferon alfa plus placebo	48 weeks	34%
Interferon alfa plus ribavirin	24 weeks	54%
Interferon alfa plus ribavirin	48 weeks	56%

Table 3. Sub group analysis – two or less predictors of good response[66]

Treatment	Duration	Sustained response rate
Interferon alfa plus placebo	48 weeks	7%
Interferon alfa plus ribavirin	24 weeks	14%
Interferon alfa plus ribavirin	48 weeks	30%

Table 4. Interferon relapsers[69]

Treatment	Duration	Sustained response rate
Interferon alfa plus placebo	24 weeks	5%
Interferon alfa plus ribavirin	24 weeks	49%

4. From life-years to QALYs

Several of the published models used utility values for the different health states in the model. These have been summarised in the following table:

Table 5. Utility values for health sates in chronic hepatitis C

	Bennett[71]	Kim[72]	Wong[73]	Baseline
Drug treatment	0.93	1	1	1
Chronic hepatitis	0.82 mild, 0.78 moderate	0.95	0.95	0.95
Cirrhosis	0.7	0.8	0.82	0.8
Ascites	0.35	0.5	0.52	0.5
Hepatic encephalopathy	0.3	0.5	0.53	0.5
Variceal bleed	0.28	0.5	0.55	0.5
After liver transplant	0.5 in first year, 0.7 after	0.8		0.8
HCC	0.1	0.25	0.55	0.25

These weights were attached to the different health states in the model to calculate a difference in quality-adjusted life-years between strategies rather than differences that only reflected mortality rates.

5. Clinical assumptions

The clinical assumptions have all been reviewed and a judgement is made on the assumption that should be used to re-run the model. Where there is uncertainty, the assumption will be slanted against drug treatment. This requires assumptions about the natural history of the disease that are relatively benign because this would reduce the benefit of drug treatment avoiding the subsequent history of the disease.

5.1 Annual progression from chronic hepatitis to cirrhosis

SHPIC assumed this to be 1.3% on the basis that progression was 20% at 15 years.
Alternative assumptions:

- Shiell[70] - 20% at 20 years i.e. 1%.
- Bennett/Wong [71,73] consider mild and moderate disease separately, annual progression from mild to moderate is 4.1% and from moderate to cirrhosis is 7.1%. While modelling in this way appears more sophisticated, the assumptions used are equivalent to a 20-year progression rate of 4.1% i.e. 0.2% per annum. Clearly this is a much lower progression rate than other studies have assumed.

New assumption: the SHPIC assumption is reduced to 1% in keeping with Scottish data from Edinburgh.

5.2 Annual progression from cirrhosis to decompensated cirrhosis

SHPIC assumed that the annual progression rate was 1.6% and that equal numbers would suffer from ascites, variceal bleed and hepatic encephalopathy.

Alternative assumptions:

- Shiell[70] - 20% at 10 years i.e. 2% per annum
- Wong [73]- 6.7% per annum
- Kim et al[72] - 4% per annum
- Bennett et al[71]- 2.5% get ascites, 1.1% get variceal bleed, 0.4% hepatic encephalopathy

New assumption: the SHPIC assumption is one of the most benign so far as disease progression is concerned, so it has been retained.

5.3 Annual progression from cirrhosis to HCC (hepatocellular carcinoma)

SHPIC assumed 2.5% per annum. This was an estimate from a range of 1-4% quoted in a clinical review.

Alternative assumptions:

- Shiell[70] - 1.4%
- Wong / Bennett[71,73] - 1.5%
- Kim[72]- 3%

New assumption: all of the figures used are consistent with the clinical paper used by SHPIC. The most benign disease assumption would be 1.4% per annum, and this was used in the re-run model.

5.4 Mortality rates from decompensated disease and from HCC

SHPIC assumed 75% annual mortality with decompensated cirrhosis and 80% with HCC.

Alternative assumptions:

- Shiell[70]- life expectancy is 2 years with both conditions
- Bennett[71] - life expectancy is 1.6 years after decompensated cirrhosis and annual mortality is 80% with HCC
- Kim[72] - annual mortality is 80% with HCC.

New assumptions: on balance, the SHPIC assumptions seem typical.

5.5 Annual rate of liver transplant with decompensated cirrhosis

SHPIC assumed 1% per annum.

Alternative assumptions:

- Shiell[70] - 2%
- Bennett[71] - 3.1%

New assumption: the models constructed in America and Australia have higher operation rates, but the treatment thresholds are likely to differ from those in Scotland. Access to surgery is more tightly restricted in the NHS than in other countries, so the SHPIC assumption seems the most plausible.

5.6 Requirement for repeat procedure

SHPIC assumed 10% of liver transplants would subsequently require a second transplant.

5.7 Age and life expectancy

SHPIC assumed the typical patient was aged 36 at diagnosis and that life expectancy at this age without the disease was 30 years. This median age was based on data from SCIEH; as it is specific to Scotland, it is retained in the present analysis.

5.8 Additional factors to be considered

The SHPIC model does not make any specific assumptions for some variables. These include:

- the rate of severe side-effects - Shiell et al[70] suggest 2%
- survival after liver transplant - in the first year Bennett et al[71] assume 21% with a rate of 5.7% in subsequent years; over a five year time horizon, this is equivalent to an annual rate of 7.5%. Kim et al[72] assumes a rate of 7% per annum.

Finally, the model had not considered the issue of identifying a high-risk group of patients suitable for treatment.

6. Rerunning the SHPIC model

To determine if the additional costs of treatment are worth the additional benefits it is necessary to perform a marginal analysis, i.e. examine the additional costs and additional benefits associated with moving from one treatment option to another.

Having changed the assumptions as described above, the results for the cohort of 1000 patients are shown in Table 6.

Table 6. Marginal analysis of different treatment options using overall sustained response rates.

Treatment programme	Total discounted costs	Additional costs	Discounted QALYS	QALYS saved	Net cost per QALY saved
Interferon naive					
Do nothing	£2,019,380		13,292		
IFN -12 months	£4,077,938	£2,058,558	13,572	280	£7,358
IFN plus R - 6 months	£5,791,717	£1,713,779	13,808	236	£7,274
IFN pus R – 12 months	£10,109,287	£4,317,570	13,925	118	£36,650
Interferon relapsers					
Do nothing more		£3,489,624		722	£4,836
IFN – 6 months	£3,139,531	£1,120,151	13,366	74	£15,214
IFN plus R- 6 months	£5,509,004	£2,369,473	14,014	648	£3,657

Abbreviations: IFN – interferon alfa, R - ribavirin

In summary

- In those patients not previously treated with interferon, the *additional* cost per QALY gained from treatment with interferon plus ribavirin (combination therapy) for 6 months compared to interferon monotherapy for 12 months was £7,274.

- In those patients not previously treated with interferon, the *additional* cost per QALY gained from treatment with combination therapy for 12 months compared to combination therapy for 6 months was £36,650. (See below for further analysis).

- In patients who relapsed after treatment with interferon, the *additional* cost per QALY gained from treatment with combination therapy for 6 months compared to no active treatment was £3,657.

The decision about duration of treatment i.e. 6 or 12 months combination therapy, is determined by a range of clinical indicators of i.e. genotype, viral load, age, level of fibrosis and sex but it was not possible to incorporate this level of detail into the model. The response rates used in the model were overall response rates from the RCTs and this should be taken into account when considering the difference in cost per QALY between 6 and 12 combination therapy. In sub-group analysis those patients with

several independent indicators of good response gain negligible benefit from the longer course of treatment of combination therapy at double the cost (54% vs. 56% sustained response). Whereas those with fewer indicators of a good response the costs are double but so are the benefits (14% vs. 30% sustained response).[66]

A simple sub group analysis was undertaken using the sustained responses from the RCT[66] and this substantially revises the additional cost per QALY saved. However such an analysis required that all the clinical variables in the model apply equally to the selected sub group of patients and the numbers in the sub groups in the clinical trials are relatively small so the results should be treated with caution. If these caveats are accepted then the results from the sub group analysis are shown in Table 7.

Table 7. Marginal analysis of different treatment option sustained response rates from using sub group analysis.

Treatment programme	Total discounted costs	Additional costs	Discounted QALYS	QALYS saved	Net cost per QALY saved
Interferon naive with three or more predictors of a good response					
Do nothing	£2,019,380		13,292		
IFN -12 months	£3,775,031	£1,755,651	13,793	501	£3,507
IFN plus R - 6 months	£5,408,035	£1,633,004	14,087	295	£5,545
IFN pus R – 12 months	£9,846,767	£4,438,732	14,117	29	£150,716
Interferon naive with two or fewer predictors of a good response					
Do nothing	£2,019,380		13,292		
IFN -12 months	£4,320,263	£2,300,883	13,395	103	£22,322
IFN plus R - 6 months	£6,215,787	£1,895,523	13,498	103	£18,389
IFN pus R – 12 months	£10,371,806	£4,156,019	13,734	236	£17,640

In summary

- In those patients not previously treated with interferon and with three or more indicators of a good response, the *additional* cost per QALY gained from treatment with combination therapy for 6 months compared to interferon monotherapy for 12 months was £5,545.

- In those patients those patients not previously treated with interferon with three or more indicators of a good response, the *additional* cost per QALY gained from treatment with combination therapy for 12 months compared to combination therapy for 6 months was £150,716 and is clearly unacceptable.

- In those patients not previously treated with interferon, with two or less predictors of a good response, the *additional* cost per QALY gained from treatment with

combination therapy for 6 months compared to interferon monotherapy for 12 months was £18,389.

- In those patients not previously treated with interferon, with two or less predictors of a good response, the *additional* cost per QALY gained from treatment with combination therapy for 12 months compared to combination therapy for 6 months was £17,640.

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