National Hepatitis C Database

for infection acquired through blood and blood products

Baseline Report

HCV
National Hepatitis C Database

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

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Health Protection Surveillance Centre
October 2007
ISBN: 978-0-9551236-2-7

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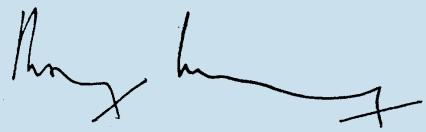
Foreword

I am delighted to introduce this baseline report of the Hepatitis C Database. This report outlines the multifaceted nature of hepatitis C in this unique group, which was infected with hepatitis C through the receipt of contaminated blood and blood products administered within this State.

I would like to congratulate the Consultative Council under whose guidance this project was initiated. I would also like to thank Dr Lelia Thornton and her team in the Health Protection Surveillance Centre (HPSC) for their work and commitment in developing the database project, maintaining it as an ongoing sustainable resource and analysing the data contained in this report. I especially want to thank the people who gave permission for their data to be included in this database. This is a reflection of their understanding of the importance of the database and their confidence in the project, particularly in light of the devastating effects hepatitis C infection has had on individuals and their families.

This report and subsequent reports will provide an invaluable resource to researchers seeking to understand the nature of the hepatitis C virus, its effects on the liver and other organs and the impact of treatment on this disease.

This database will not only facilitate research. It will also inform clinical practice and enable more effective service planning for the emerging needs of this group. I look forward to a promising future for this database and can guarantee the continued support of my Department and the Health Service Executive.



Mary Harney, T.D.
Minister for Health and Children

Acknowledgments

We would like to extend our sincere thanks to those people who consented to be included in this database.

We would also like to thank the staff of the eight hepatology units who gave generously of their time, experience and support to make this project possible. In particular we wish to acknowledge the consultant hepatologists, administrative staff, hepatitis C liaison nurses and consultant histopathologists who contributed to this project.

The four patient support groups (Positive Action, Transfusion Positive, Irish Haemophilia Society and Irish Kidney Association) actively encouraged their members to participate and were very helpful in advising at all stages of the project.

Helpful advice and support was provided by the Database Steering Committee and by the Scientific and Technical Group, all of whom gave generously of their time. Their members are listed in appendices A and B.

Thanks are also due to Professor Hannah McGee, Royal College of Surgeons in Ireland; Dr Emer Lawlor, Irish Blood Transfusion Service; Dr Jeff Connell, National Virus Reference Laboratory; Dr Niamh Nolan, St Vincent's University Hospital; Dr Barry White, St James's Hospital; Dr Liam Fanning, Cork University Hospital; Ann McGrane and Mary Jackson, Department of Health and Children; Tom Maguire, Office of the Data Protection Commissioner; Fiona Mulvany, Health Research Board; Dr Elizabeth Kenny, Chair of Consultative Council on Hepatitis C; staff of the General Registry Office (GRO); and the Hepatitis C Liaison Officers, HSE, for their assistance.

Aline Brennan, Aileen Murphy, Lisa Slattery and Kate Hunter all formerly worked on the database in HPSC and contributed enormously to its development. HPSC staff, in particular Myles Houlden, Dr Darina O'Flanagan, Dr Derval Igoe, Orla Bannon, Maurice Kelly and Sean Flood provided invaluable support on administrative, IT, communications and scientific matters.

Finally we would like to thank Dr Helen Harris and Dr Mary Ramsay of the UK National Hepatitis C Register for their advice and guidance in the setting-up phase of the database.

HPSC National Hepatitis C Database Team
Dr Lelia Thornton, Specialist in Public Health Medicine (Project Co-ordinator)
Niamh Murphy, Surveillance Scientist
Margaret McIver, Surveillance Assistant
Paula Flanagan, Research Nurse
Sarah Gavin, Database Developer

Hepatology Units
Beaumont Hospital, Dublin
Cork University Hospital
Mater Misericordiae University Hospital, Dublin
Our Lady's Children's Hospital, Crumlin, Dublin
St Luke's Hospital, Kilkenny
St James's Hospital, Dublin
St Vincent's University Hospital, Dublin
University College Hospital, Galway

Executive Summary

Background

Hepatitis C infection has emerged over the last two decades as a major cause of illness and death worldwide. Sixty to eighty five percent of hepatitis C infected people develop chronic infection. A proportion of people with chronic infection develop progressive liver fibrosis, usually after 20-30 years, which may lead to cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). However, with the advent of new drug therapies the disease can now be treated successfully in many people. As hepatitis C virus was first identified as recently as 1989, many aspects of the disease in terms of its natural history, factors associated with disease progression, and response to treatment remain to be clarified.

The National Hepatitis C Database was established to gather important information on an ongoing basis on a group of people with hepatitis C infection acquired through blood or blood products in Ireland. These include women infected through anti-D immunoglobulin, recipients of blood transfusion, people with haemophilia and other blood clotting disorders and people who received treatment for renal disease. The fact that most of these people have a known date and source of infection and also that they are being regularly followed up through a small number of specialist services allows a unique opportunity to carry out internationally significant research into both the natural history of hepatitis C and its treatment. Collection of information about the use and outcome of investigative and treatment services will also allow for planning of appropriate services for the future.

This report describes the development of the database, the process of recruitment and data collection, and the main findings of the baseline data collected on participants.

National hepatitis C database

The database was developed by the Health Protection Surveillance Centre (HPSC) in association with the eight designated hepatology units. The project is overseen by a Steering Committee, under the auspices of the Consultative Council on Hepatitis C, and advised by a Scientific and Technical Group.

The computer application for the database was purpose-built to meet current needs and allow for future modification if required. A high level of security is ensured, and approved by external audit. The database was upgraded in 2007 to a web-technology based system to enhance its usefulness and efficiency.

Any person (alive or dead) who contracted hepatitis C infection through the administration of blood or blood products within the state is eligible to be included in the database. Hepatitis C infection is defined as the detection of hepatitis C specific antibodies or the detection of hepatitis C nucleic acid. Eligible patients are identified by the eight specialist hepatology units.

Information is collected only on eligible people who consent to participate in the database and on eligible patients who have died. Information is gathered from the patient's medical records (hospital charts) in the eight hepatology units and will be updated on an annual basis. No direct contact is made with any patients. No patient names or addresses are recorded in the database. Approval was obtained from the ethics committees of all eight hospitals and from the Office of the Data Protection Commissioner.

The starting point for this database was to determine the total number of eligible participants. This was done by amalgamating and cross-checking lists of patients from all eight hepatology units to ensure there was no duplicate counting. Although there had been estimates of the size of this group, and of sub-groups of it, published previously, this is the first time that an exercise has been carried out to definitively count people. The only members of the cohort not included in this number are those who never attended one of the hepatology units, either by choice, because they lived abroad, or had died before the services were set up. These numbers are likely to be low.

The database population includes those who had any hepatitis C antibody positive result, even if this was only a weak positive screening test or a confirmatory test of indeterminate result. The reasons for including non-confirmed cases are explained in the report. However, where it is appropriate, data analysis can be confined to those having a confirmed test.

Baseline Data Collection

Patient recruitment began in the first week of August 2004. The consultant hepatologist in each hepatology unit wrote to each eligible patient inviting them to participate. A research nurse from HPSC carried out the data extraction in the hepatology units. The data collection was done in 2005 and 2006, followed by data validation up to June 2007. Information in the following categories was collected: demographic and lifestyle data, hepatitis C infection details, current clinical status, clinical management, test results and treatment details.

Main findings

- The total number in the eligible population was 1,634. The baseline cohort, comprising those who consented and those who had died, was 1,192 or 73 percent of those eligible. By source of infection, the largest group was anti-D recipients (770, 65%), followed by blood transfusion recipients (284, 24%), recipients of treatment for blood clotting disorders (107, 9%) and people who received treatment for renal disease (25, 2%).

- Older age groups were more likely to participate. Those with blood clotting disorders were significantly less likely to participate. Over 80 percent of the 1,192 participants are female, reflecting the large group infected through anti-D immunoglobulin. Most participants are now aged between 40 and 65 years.

- The average age at infection was 28 years but varied by source of infection. Seventy six percent of the cohort has now been infected for 20 years or more. The literature suggests that disease may progress particularly between 20 and 30 years after infection so follow up over the next decade will be important.

- A total of 63 percent had at some time tested polymerase chain reaction (PCR) positive, indicating active infection. Of the whole cohort, 79 percent had had a confirmatory test positive for hepatitis C. The anti-D recipient group had the lowest level of confirmed positive results (72%) and the lowest percentage of patients who ever tested PCR positive (53%).

- Of those tested for genotype, three quarters of all participants, and 90 percent of the anti-D group, were genotype 1. Genotype 1 is associated with a less successful response to anti-viral treatment.

- Ten percent had indicators of excess alcohol consumption. Alcohol intake information was infrequently recorded except at the first visit. Alcohol excess was more prevalent in men. Alcohol is an important factor in the progression of hepatitis C liver disease.

- Thirty one (29%) blood clotting disorder patients were co-infected with HIV. Co-infection with HIV has been shown to accelerate progression of hepatitis C infection.

- Ten percent of patients had signs of liver disease recorded in their charts and the vast majority of these patients were PCR positive. These signs were more common in males (22%) than females (7%).

- Liver enzyme (ALT and AST) levels were abnormally elevated in about half of all PCR positive patients, and elevated levels were associated with longer duration of infection.

- Alpha fetoprotein (AFP) levels were abnormally high for 11 percent of the total cohort and for 15 percent of PCR positive participants. Male patients, patients with longer duration of infection and

those with cirrhosis were more like to have elevated AFP levels. AFP is used as a marker for hepatocellular carcinoma but is not specific for this.

- Almost all patients had other significant medical conditions described in their charts. These are not necessarily diagnosed according to standardised criteria and may be unrelated to hepatitis C infection. The most commonly recorded conditions were fatigue and lethargy (30%), depression (27%) and arthralgia and joint pain (24%). Fatigue or lethargy were more likely to be reported for females and were slightly more likely in patients who tested PCR positive at some stage. Depression was also more likely to be reported for females and for those who tested PCR positive. Twenty three percent of women had a hysterectomy or related operation. Without a comparison group, it is not possible to determine if the prevalence of these conditions is different from the general population.

- Eighty four percent of PCR positive patients had had a liver biopsy, although this figure was lower for the blood clotting disorder group at 33 percent.

- Twenty one percent of those who were PCR positive and had a liver biopsy had moderate or severe inflammation on the most recent biopsy. Patients who consumed alcohol in excess, those who were infected for longer durations, and older patients, were significantly more likely to have moderate or severe inflammation on biopsy. Fifteen percent of the anti-D group, 28 percent of the blood transfusion group, 17 percent of the blood clotting disorder group and 21 percent of renal patients had either moderate or severe inflammation.

- High fibrosis scores on liver biopsy (3/4 using 0-4 scoring systems or 4/5/6 using 0-6 scoring systems) were less prevalent in the anti-D group (8%) than in the other groups: blood transfusion (28%), blood clotting disorder (21%), renal (20%). This may be related to sex, as 28 percent of males biopsied had high fibrosis scores compared to 11 percent of females. Patients who consumed alcohol in excess, were older at infection and who had been infected for longer durations were also more likely to have high fibrosis scores.

- Cirrhosis was found in 74 patients (6%). There was variation in the proportion of patients with cirrhosis in the four patient groups, with blood transfusion patients significantly more likely to have cirrhosis. Ninety seven percent of those with cirrhosis were PCR positive. Patients aged over 60 years at last visit to the hepatology unit and those with excess alcohol consumption were also more likely to have cirrhosis.

- Ten patients had hepatocellular carcinoma, nine of whom had died. All were PCR positive.

- One hundred and eleven patients (9.3%) had died. Death was directly due to liver disease in 29 (27%). Of these, 18 (62%) also had evidence of excess alcohol intake, and 26 (90%) were PCR positive. Overall, the risk of death was higher in males, PCR positive participants and those who were older at the time of infection, and lower in the anti-D group.

- On most outcome measures, anti-D patients had more favourable results than the other three patient groups. Similarly, outcomes for females were more favourable than for males.

- Only 37 percent of PCR positive patients had ever received anti-viral treatment to date. Patients with genotypes 2 or 3 were more likely to be treated. Those in the blood clotting disorder and blood transfusion groups were more likely to have been treated, as were males. The sustained virologic response (SVR) to the first course of treatment with combination therapy of pegylated interferon and ribavirin was 29 percent for genotype 1 and 71 percent for genotype 2 or 3 patients. However, the number of patients treated initially with this regime was low and thus the results may not be representative. Follow up of treatment data and responses over the next few years will be of great interest as more patients are likely to opt for treatment.

- The most common long-term medications used were cardiovascular drugs, drugs used to treat depression, anxiety and sleep disorders, drugs for acid-related disorders and anti-inflammatory and anti-rheumatic drugs. However, it is not possible to interpret the significance of these data without comparing them to usage figures in the general population.

- **Complementary and alternative therapies are increasingly being used and were recorded in the charts of 66 patients. The ones most commonly used include herbal remedies, acupuncture and massage. The proportion of patients using these therapies is likely to be underestimated in the database as many patients attend private practitioners.**

- **Ten participants have received liver transplants to date. All were PCR positive. The mean duration of hepatitis C infection at transplant was 27 years.**

- **Six percent of live participants had in-patient stays for hepatology-related care during the previous 12 months. Liver biopsy was the most common reason for admission.**

- **Seventy four percent of live participants attended an outpatient appointment for hepatology-related care during this period. The median number of appointments was two.**

- **Four hundred and forty five patients (41 percent of live patients) used specialist health services in the previous 12 months. The most common services attended related to psychiatry, psychology or counselling.**

- **Of the total cohort, 49 percent remain chronically infected. But of those who had a confirmed positive test, 62 percent remain chronically infected and a further 13 percent had cleared the virus following treatment.**

Summary tables of the main outcomes may be found at the end of this executive summary. More detailed results are contained in Chapter 4 of the report.

Discussion

The baseline participation rate of more than 70 percent is good. This response is a tribute to the generous co-operation of the participants, support groups, and staff in the hepatology units. However, we hope to improve this level of participation over the next few years.

The database contains a large amount of comprehensive and relevant data on over one thousand people infected with hepatitis C. These data will be updated every year so that long-term follow up can be done. Although all participants are considered to be in the cohort of people infected through blood and blood products, they do not form a homogeneous group in many respects, such as age at acquisition, sex, co-morbid conditions and genotype, and much of the data are more appropriately analysed in four groups determined by source of infection.

In general, the quality and completeness of the data in the database is good, with few missing data in important areas of outcome. One of the main concerns about quality of data was in relation to the year of acquisition of infection, which was not known for some participants. In order to follow the progression of disease forward in time, it is essential to know the starting point. The source of infection was also uncertain for a number of people who had more than one exposure. It may be possible to improve the quality of this information in the future by closer linkage between the hepatology units and bodies having definitive data such as the National Virus Reference Laboratory (NVRL), the National Centre for Hereditary Coagulation Disorders (NCHCD) and the Irish Blood Transfusion Service (IBTS). However, within the overall group, there are large cohorts with certain dates and sources of infection and these can be researched more thoroughly.

Another area of concern about missing data is in the recording of alcohol consumption, and the person's height and weight, to allow for calculation of body mass index (BMI). Given the association between both alcohol intake and obesity on the progression of liver disease, it is essential that these be recorded in a systematic way at routine clinic visits. Recording of hepatitis B infection and vaccination status was also poor and should be improved.

Examination of liver biopsies yields important information about disease progression. The database contains the inflammatory grade and fibrosis score for each biopsy performed on each of the participants, if recorded in the hospital chart. However, the fibrosis scoring system was not standardised throughout all hospitals and thus not all results could be collated for analysis. There is also a subjective element in reporting biopsy results. For these reasons, it may be useful to consider the approach taken by the National HCV Register in the UK where there is centralised archiving and scoring of liver biopsies.

There are limitations inherent in this database, given its design. As the information comes only from what is recorded in hospital medical records, it is inevitable that some data are missing or not recorded consistently by different units. We endeavoured to standardise the collection of data by having a trained research nurse do the data extraction according to written guidelines. However, particularly in areas like clinical signs and symptoms, and diagnoses of medical conditions, the data are generally not recorded in a standardised way and will vary considerably from one unit to another. So, although our findings in these areas may be of some interest, special additional studies would be needed to investigate them further. In addition, information on services attended privately will not be recorded in the database. In particular, this is likely to lead to an underestimate of the use of alternative treatments.

Another limitation in the use of the database is the lack of a comparison group of non-hepatitis C infected people. For the main findings we have made comparisons between PCR positive and PCR negative participants. However, non-infected comparison groups, similar to the cases in other respects such as age and sex, are needed in order to interpret many of the findings. This is an area that should now be pursued.

Next steps for the database

Feedback to participants and professionals is essential in ensuring ongoing co-operation and commitment to this project. The findings must also be brought to the attention of those involved in patient care and planning of services for this patient group. It is also important that significant findings are made available to the international scientific community. This report will be made freely available through the hepatology units, patient support groups, hepatitis C liaison officers and HPSC. It will be available electronically on the HPSC website. An annual newsletter will be published for participants and other eligible people. An annual report will be prepared each year presenting the data gathered in the follow-up data collection. This report and subsequent reports will be made available to health service managers and others involved in the planning and evaluation of health services. Papers will be prepared for submission to peer-reviewed scientific journals.

One of the objectives of the database is that it should serve as a resource for research into hepatitis C. Given the commitment by patients and health professionals alike to the development of this project, we hope that the database will be used to its full potential. An annual call for research based on the database will be issued and overseen by the Database Steering Committee. Researchers may be interested in further analysing the data or in using the database to facilitate special additional studies. Each hepatology unit will be given access to the full dataset relating to their patient group, and access to the complete database except for individual and unit identifiers. This will facilitate individual units to carry out their own research. The selection of appropriate comparison groups will now be investigated. These are necessary in order to determine the significance of many of the findings in hepatitis C infected people.

We will continue to work to improve the database in terms of both participation rate and quality of the data. The aim is to improve the participation rate to at least 90 percent. Very few of those who are not participating have actually refused to consent, rather they have not responded to the invitation. We hope that by demonstrating the work already done we may engender confidence and show the usefulness of the database, and thus encourage non-responders to consider participating now. For people who would like to participate and have not yet consented, consent forms are available through the hepatology units.

The first year of annual follow-up will be 2007. This data collection is already well underway by a database research nurse. An annual report will be produced in 2008.

In 2007, the database was upgraded to a web-technology based system allowing the entry of data by a database research nurse to be completed on-site in the hepatology units and so reduce the need for paper forms. This system will also allow staff at the hepatology units to view data entered for their patients. It is proposed that an automated interface to each hospital laboratory system be developed in the future to allow the electronic collection of information.

Conclusion

This report demonstrates the type of data contained within the database and the potential for its use by others. There is a considerable amount of information available to be further analysed and interrogated. It will be updated and improved annually. One of the purposes of the database is to facilitate research into hepatitis C. What is presented here is simply a starting point and we hope it will stimulate research questions that may be investigated within the framework of the database project.

The database will allow us to follow this group of people with hepatitis C infection over time in order to better describe the natural history of the infection and to elucidate factors associated with disease progression and successful response to treatment. It will also provide valuable information for planning health services for the future. The success of the project to date is a measure of the interest among people with hepatitis C and health professionals in furthering knowledge about the infection and in helping to plan services for the future. It also indicates the willingness of patients and health professionals to work together in partnership for the good of all.

Summary tables of main outcomes

Table 1. Number and percentage of patients with key outcomes by PCR status

Summary of main outcomes	Number of patients (%)	Number ever tested PCR positive (%)	Number with no positive PCR results (%)
Total patients	1192	746 (62.6)	446 (37.4)
Signs of liver disease	114 (9.6)	107 (14.3)	7 (1.6)
Extrahepatic manifestations of hepatitis C	100 (8.4)	76 (10.2)	24 (5.4)
Biopsied and had moderate/severe inflammation at last biopsy	132 (18.2)	130 (21.3)	2 (1.7)
Cirrhosis on biopsy or elsewhere in chart	74 (6.2)	72 (9.7)	2 (0.4)
Liver tumours or HCC	10 (0.8)	10 (1.3)	0
Deceased	111 (9.3)	92 (12.3)	19 (4.3)
Liver-related disease directly caused death	29 (2.4)	26 (3.5)	3 (0.7)
Liver-related disease contributed to death	32 (2.7)	27 (3.6)	5 (1.1)

Table 2. Summary of current hepatitis C status of cohort

Current status	Living patients	Deceased patients	All patients	% of patients	Confirmed positive patients	% of confirmed positives
Remain chronically infected (PCR positive)	500	84	584	49.0	584	62.3
Cleared virus without treatment*	444	23	467	39.2	212	22.6
Treated and cleared virus	120	3	123	10.3	123	13.1
Still on treatment	17	1	18	1.5	18	1.9
Total	**1081**	**111**	**1192**	**100**	**937**	**100**

*5 of the patients who were treated had no positive PCR results in their medical records

The current status for the cohort is based on their last test results. This was applied to deceased patients in the same way as living patients and indicates their last known status. “Still on treatment” indicates that the patient was on, or just finished treatment, when their last PCR test was done and thus their status could not be determined.

Table 3. Summary of main outcomes for anti-D patients

Summary of main outcomes	Number of patients	% of patients
Total patients	770	100
Ever PCR positive	409	53.1
Confirmed positive (PCR or RIBA positive)	553	71.8
Signs of liver disease	37	4.8
Extrahepatic manifestations of hepatitis C	59	7.7
Biopsied and had moderate/severe inflammation at last biopsy	71	14.5
Cirrhosis on biopsy or elsewhere in chart	26	3.4
Liver tumours or HCC	2	0.3
Deceased	34	4.4
Liver-related disease directly caused death	7	0.9
Liver-related disease contributed to death	10	1.3

Table 4. Summary of current hepatitis C status of anti-D patients

Current hepatitis C status	Living patients	Deceased patients	All patients	% of patients	Confirmed positive patients	% of confirmed positives
Remain chronically infected (PCR positive)	320	20	340	44.2	340	61.5
Cleared virus without treatment	363	12	375	48.7	158	28.6
Treated and cleared virus	46	1	47	6.1	47	8.5
Still on treatment	7	1	8	1.0	8	1.4
Total	**736**	**34**	**770**	**100**	**553**	**100**

Table 5. Summary of main outcomes for blood transfusion patients

Summary of main outcomes	Number of patients	% of patients
Total patients	284	100
Ever PCR positive	225	79.2
Confirmed positive (PCR or RIBA positive)	252	88.7
Signs of liver disease	56	19.7
Extrahepatic manifestations of hepatitis C	31	10.9
Biopsied and had moderate/severe inflammation at last biopsy	52	28.3
Cirrhosis on biopsy or elsewhere in chart	39	13.7
Liver tumours or HCC	6	2.1
Deceased	52	18.3
Liver-related disease directly caused death	16	5.7
Liver-related disease contributed to death	12	4.3

Table 6. Summary of current hepatitis C status of blood transfusion patients

Current hepatitis C status	Living patients	Deceased patients	All patients	% of patients	Confirmed positive patients	% of confirmed positives
Remain chronically infected (PCR positive)	123	42	165	58.1	165	65.2
Cleared virus without treatment	54	8	62	21.8	31	12.3
Treated and cleared virus	50	2	52	18.3	52	20.6
Still on treatment	5	0	5	1.8	5	2.0
Total	**232**	**52**	**284**	**100**	**253**	**100**

Table 7. Summary of main outcomes for blood clotting disorder patients

Summary of main outcomes	Number of patients	% of patients
Total patients	107	100
Ever PCR positive	85	79.4
Confirmed positive (PCR or RIBA positive)	104	97.2
Signs of liver disease	17	15.9
Extrahepatic manifestations of hepatitis C	6	5.6
Biopsied and had moderate/severe inflammation at last biopsy	5	16.7
Cirrhosis on biopsy or elsewhere in chart	7	6.5
Liver tumours or HCC	2	1.9
Deceased	13	12.2
Liver-related disease directly caused death	4	3.8
Liver-related disease contributed to death	5	4.7

Table 8. Summary of current hepatitis C status of blood clotting disorder patients

Current hepatitis C status	Living patients	Deceased patients	All patients	% of patients	Confirmed positive patients	% of confirmed positives
Remain chronically infected (PCR positive)	43	11	54	50.5	54	51.9
Cleared virus without treatment	22	2	24	22.4	24	23.1
Treated and cleared virus	24	0	24	22.4	21	20.2
Still on treatment	5	0	5	4.7	5	4.8
Total	**94**	**13**	**107**	**100**	**104**	**100**

Table 9. Summary of main outcomes for renal patients

Summary of main outcomes	Number of patients	% of patients
Total patients	25	100
Ever PCR positive	24	96.0
Confirmed positive (PCR or RIBA positive)	24	96.0
Signs of liver disease	4	16.0
Extrahepatic manifestations of hepatitis C	4	16.0
Biopsied and had moderate/severe inflammation at last biopsy	4	21.1
Cirrhosis on biopsy or elsewhere in chart	2	8.0
Liver tumours or HCC	0	0
Deceased	11	44.0
Liver-related disease directly caused death	1	4.0
Liver-related disease contributed to death	5	20.0

Table 10. Summary of current hepatitis C status of renal patients

Current hepatitis C status	Living patients	Deceased patients	All patients	% of patients	Confirmed positive patients	% of confirmed positives
Remain chronically infected (PCR positive)	12	10	22	88.0	22	91.7
Cleared virus without treatment	2	1	3	12.0	2	8.3
Treated and cleared virus	0	0	0	0	0	0
Still on treatment	0	0	0	0	0	0
Total	**14**	**11**	**25**	**100**	**24**	**100**

Chapter 1 Introduction

Background

It is estimated that over 1,600 people have been infected with hepatitis C virus through the administration of contaminated blood and blood products in Ireland. These include women infected through anti-D immunoglobulin, recipients of blood transfusion, people with haemophilia and other blood clotting disorders, and people who received treatment for renal disease.[1]

In early 1994, it was discovered that anti-D immunoglobulin contaminated with hepatitis C had been administered to a number of women between 1977 and 1979 and between 1991 and 1994. In February 1994, the Irish Blood Transfusion Service (IBTS) (formerly BTSB) instituted a national hepatitis C screening programme for all women who had received anti-D between 1970 and 1994.[2] A further targeted lookback programme was implemented at the start of 1995 to trace donors and recipients of potentially infected blood. This was followed up by an optional programme in September 1995 as not all recipients could be traced by the targeted lookback.[3]

Specialist hepatology services were set up in eight designated hospitals to provide services for this group who acquired hepatitis C infection within the state through contaminated blood and blood products. They are also entitled to a range of additional hospital and primary health care services under the Health (Amendment) Act, 1996. Eligible persons are issued with a Health Amendment Act (HAA) card, which facilitates the holder to access these services.

In 1996, the Consultative Council on Hepatitis C was established to advise the Minister for Health on all matters relating to hepatitis C. In March 2000, the Council published a review of health services available for persons who contracted hepatitis C through the administration within the state of blood or blood products. One of the recommendations of this review was “that a national database be established for research purposes; this to be located at an independent coordinating agency and run in association with relevant groupings”.[1] The Health Protection Surveillance Centre (HPSC) (formerly NDSC) was given the responsibility of developing this database. This report describes the development of the database and presents the data collected in the first round of data collection.

Hepatitis C

Hepatitis C infection is a major cause of chronic liver disease and death throughout the world, with more than 170 million people chronically infected.[4] Hepatitis C virus was first identified in 1989 and commercially available tests to identify it were developed in 1991. Hepatitis C was found to account for the majority of infections previously categorised as “non-A, non-B hepatitis”.[5] There are six hepatitis C genotypes and more than 50 subtypes.

Hepatitis C is transmitted primarily through exposure to contaminated blood or blood products, most commonly through contaminated needles and syringes. With the advent of routine blood screening for hepatitis C antibodies in 1991, transfusion-related hepatitis C has almost disappeared. At present, injecting drug use is the most common risk factor.[6,7] The risk of vertical transmission from mother to baby seems to be low (<6%) and sexual transmission plays a limited role.[5,8] Other less common routes of transmission include haemodialysis, organ transplantation, and tattooing.

Initial hepatitis C infection is asymptomatic or mild in over 90% of cases. Most studies have shown that 60-85 percent of hepatitis C infected people develop chronic infection. A proportion of people with chronic infection develop progressive liver fibrosis, which may lead to cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). Estimates of the proportion of chronically infected persons who develop cirrhosis 20 years after infection vary widely from 2 to 4 percent in children and young women to 20 to 30 percent in middle-aged transfused subjects. The median time from acquisition of the virus to cirrhosis has

been estimated to be 30 years.[9] Factors clearly associated with fibrosis progression include duration of infection, older age at infection, male sex, alcohol consumption, HIV co-infection, and hepatitis B co-infection. Metabolic disorders such as being overweight and diabetes are emerging as independent co-factors of fibrogenesis.[5,6,7,8] There is conflicting evidence as to whether viral load or genotype affect the risk of disease progression.[5] The estimated annual risk of HCC in patients with cirrhosis is 1 to 7 percent.[5]

There have been important advances in the treatment of hepatitis C infection in the past decade, both in terms of viral eradication and improved histology.[6,7,9] Combination regimens of pegylated interferons and ribavirin, introduced in 2001, induce a sustained response in 42-82% of patients with chronic hepatitis C, depending on genotype. There are early indications that interferon-based regimens improve the prognosis of chronic hepatitis C patients who respond to therapy.[8]

Chapter 2 National Hepatitis C Database

The national hepatitis C database for infection acquired through blood and blood products has been set up by HPSC in association with the eight designated hepatology units. This database is supported financially by the Health Service Executive (HSE) and formerly by the Department of Health and Children (DoHC).

The objectives of the database are:

1. To follow the natural history of infection in this group of people
2. To evaluate the impact of various host factors on the progression of the disease
3. To evaluate the outcomes of treatment
4. To monitor the uptake of services
5. To provide information for the planning and evaluation of health services
6. To serve as a resource for future research into hepatitis C

Hepatitis C project management

The development and management of the database project is overseen by a Steering Committee. Members of the committee include representatives of the four patient support groups, the DoHC and the HPSC team, a consultant hepatologist, a hepatology nurse, a hepatitis C liaison officer, a clinical psychologist and a director of public health. The members are listed in appendix A.

In addition, a Scientific and Technical Group was set up to support and advise HPSC on the scientific and technical development of the database and to monitor its operation. It mainly represents the healthcare professionals who will contribute to and use the system including the consultant hepatologists from the eight designated hepatology units. The members are listed in appendix B.

Database population

Any person (alive or dead) who contracted hepatitis C infection through the administration of blood or blood products within the state is eligible to be included in the database. These include women infected through anti-D immunoglobulin, recipients of blood transfusion, people with haemophilia and other blood clotting disorders and people who received treatment for renal disease. For the purpose of this database, hepatitis C infection is defined as the detection of hepatitis C specific antibodies or the detection of hepatitis C nucleic acid. This includes all those who are ELISA (enzyme linked immunosorbent assay)/EIA (enzyme immunoassay) positive or weak positive, recombinant immunoblot assay (RIBA) positive or indeterminate, or hepatitis C polymerase chain reaction (PCR) positive. Eligible patients are identified by the eight specialist hepatology units.

Source of data

Data are collected on eligible people who consent to participate in the database and on eligible people who have died, providing no objections are made by the relatives of the deceased people. Data contained in the database are gathered from the patient's medical records (hospital charts), or existing databases, in the eight hepatology units. Data will be updated on an annual basis. No direct contact is made with any patients for the purpose of collecting data for the database. No patient names or addresses are recorded in the database. Data held by the HPSC are anonymised to the extent that only initials and dates of births are held. Approval was obtained from the ethics committees of all eight hospitals and from the Office of the Data Protection Commissioner.

Database development

This section describes the computer applications that comprise the physical (technical) database. The brief for this was to build a system, which would:

- Allow HPSC staff to input information compiled by the research nurse
- Force the user to double-enter each piece of information (to prevent errors)
- Be user-friendly, minimise typing
- Store the data in a format which could be used readily for analysis
- Enforce security measures to ensure that access to view and change data was defined for each role within the team.

Two of the hepatology units had a computerised system in place, so computerised interfaces were built to allow information from each to be imported into the main database. At the end of each data collection, a snapshot of the database was required to facilitate report building and to create a digital history of the database. Finally, a mechanism to create electronic copies of the database (for research purposes) was created.

This database was initially built using MS SQL Server 2000 to house the database and core functionality, and accessed by the user via an MS Access 2000 client. It was upgraded in 2007 to a web-technology based solution. The diagram in appendix C describes the system as it was when baseline data were collected.

A software package called Business Objects was used to facilitate analysis and reporting of the data. A reporting database was built first using MS SQL Server - this gathered and presented the data for reporting. A number of universes (Business Objects reporting structures) were built to allow the database to be queried for both reporting and analysis, and day-to-day operational queries.

Security was enforced using a combination of network, SQL Server and MS Access security and permissions. Access to the database and permissions to edit data are allocated on a ‘least privilege required’ principle.

At the end of baseline data collection, a snapshot was taken of the database and a Business Objects reporting universe set up to allow queries to be performed on this.

The database’s physical location is in a secure computer room in the HPSC, with access strictly limited to key technical support staff.

Chapter 3 Baseline Data Collection

Patient recruitment

The eight hepatology units were asked to compile a list of all eligible patients (as defined in chapter 2) who could potentially be included in the database. The patient's consultant ultimately determined their eligibility. To allow potential duplicates of participants between units to be identified, the lists of patients' initials and dates of births from each unit were sent to the HPSC and compared. When queries relating to possible duplicates arose, the relevant hepatology units were contacted. They investigated the patients and established if they were true duplicates and, if so, which unit was currently responsible for their care. The revised list formed the basis for the population to be invited to participate in the database.

Patient recruitment began the first week of August 2004 through each of the eight hepatology units. The consultant hepatologist in each unit wrote to each eligible patient, explained the purpose of the database and invited them to participate (appendix D). An information leaflet and the consent form were enclosed with this letter (appendices E and F). One reminder letter was sent out in mid-October 2004 to patients who did not respond to the initial letter. The patient support groups encouraged their members to participate through their newsletters and at meetings. Patients were also encouraged to participate as they attended the hepatology unit for routine visits.

Deceased patients

In relation to eligible deceased people, a notice was placed in the national media informing families of deceased people that a database would collect information from the hospital records of deceased people who had contracted hepatitis C through the administration of blood products within the state. The notice provided contact details for the support groups and the hepatology units, and families were invited to contact them to discuss any queries they might have had regarding the database. They were entitled to refuse participation on behalf of their deceased family member. The collection of data on deceased people began two weeks after the notice was placed. No family member refused participation in the database. Patients who died after refusing to participate in the database were not included.

Patient consent

Patient consent was verified prior to recording the patient's information. If the consent 'yes/no' boxes were not ticked, the designated unit coordinator contacted the patient to verify consent. The database identification (ID) number, initials and date of birth were entered into the space provided at the end of the front and back copies of the database consent form by the staff of the hepatology unit or by the research nurse. The back copy of the consent form was sent to HPSC at the same time as the data collection form for that participant. The front copy was filed in the participant's medical notes with a copy of the completed baseline data collection form. The back copy of the consent form only included the patient's initials, database ID number, date consent signed and date of birth (appendix F). A photocopy of the patient consent form is stored in the hepatology unit in a central file.

For patients under the age of 16 years, parental consent only was required. For those aged 16 and 17 years, consent forms were signed by both the patient and their parents. However, if the parent did not wish to ask the child to sign the consent form, the parental consent was sufficient.

Data collection

Data were collected only on persons who consented to participate in the database and deceased persons. A patient registration form (known as the baseline form) was used for manual extraction of data from the medical records in the hospital of the hepatology unit most recently attended by each patient (appendix G).

A research nurse from HPSC carried out the data extraction in the hepatology units. A handbook was devised to assist and standardise data extraction and data entry.

The baseline data includes all relevant information from each participating patient's medical chart relating to visits and tests on or before 31st December 2005. Patients who were eligible and diagnosed prior to 31st December 2005 and for whom data were collected prior to the 31st October 2006, were included in the baseline data collection. The majority of data collection was done in 2005. The remainder of data collection was done in 2006, followed by data validation up to June 2007. Information on eligible patients who consented after October 2006 and those who were diagnosed after the end of 2005 will be collected in the follow up stage, which commenced in January 2007.

Data were also extracted from two existing databases in two of the units. In each case, a computer application was built by HPSC to extract the required information from the databases and compile an electronic file of data – an interface file. This interface file was then uploaded into the HPSC database so that the electronically-collected information could be applied to the relevant patient records. The units' databases did not contain all the information required by the National Hepatitis C Database so the remaining data were collected by the HPSC research nurse.

The following categories of information are collected on the baseline form (appendix G):

- Demographic and lifestyle data
- Hepatitis C infection details
- Current clinical status
- Clinical management
- Test results
- Treatment details

Data entry

Once the data collection forms were completed by the research nurse, the forms were given to the surveillance assistant in HPSC. Data were entered onto the database by a surveillance assistant. Double entry was used to maximise accuracy.

The original baseline data collection forms were then filed in a secure locked cabinet in HPSC. Access to this cabinet is provided to authorised personnel only. Any queries that arose during data entry, and where information was missing from various fields, were directed to the research nurse, who followed these up with the appropriate staff in the hepatology units.

Ineligible patients

Patients who had consented but were later found to be ineligible were removed from the database. The consultant hepatologists were informed of this and asked to contact these persons and inform them that they were no longer included in the database as they were not eligible.

Assumptions

Various assumptions were made where data were missing and these related mainly to the year of infection. These assumptions were:

- Anti-D: If the person had received anti-D on multiple occasions, and one of these was the year of an outbreak period, i.e. 1977-1979 or 1991-1994, this year was taken as the year of infection. If none of the years fell into either of the outbreak periods, the earliest year that anti-D had been administered was used as the year of infection.

- Blood transfusion: If the person had received multiple blood transfusions and none of them had been identified as being infectious, the earliest transfusion year was taken as the year of infection.

- Clotting factor concentrates: For people with haemophilia and other blood clotting disorders, if the year of infection was not available, the year that the patient first received factor concentrate was used as a proxy for the year of infection. Where the year of infection and the year of first factor administered were missing, then the year of diagnosis of haemophilia was used for the year of infection.

- Renal: This category includes patients who received treatment for end stage renal disease, including dialysis, blood transfusion and renal transplant, without identifying which treatment was responsible for the hepatitis C infection. The year of starting dialysis or of first blood transfusion, whichever was the earlier, was used as an estimate of the year of infection.

- If the patient had multiple potential exposures, tested negative for hepatitis C after one or more and subsequently tested positive, then the date of the first exposure after the last negative test was taken as the date of infection.

- Where precise data were missing involving dates (e.g. date of infection), the year of infection was converted to 02/07/YYYY, where YYYY was the year of infection and 02/07 was the midpoint of the year. All ages calculated were truncated and all durations were rounded based on the outcome of the calculation.

Liver biopsies

Several different scoring systems were used to stage and grade the hepatitis C liver biopsies in the eight hepatology units. The main liver biopsy scoring systems that were used by the consultant histopathologists for the scoring of the hepatitis C cohort were:

- Knodell system: fibrosis scored from 0-4 [10]
- Modified Knodell system, also known as the Ishak or modified HAI system: fibrosis scored from 0-6 [11,12]
- Scheuer system: fibrosis scored from 0-4 [13]
- International Group of Hepatopathologists system: fibrosis scored from 0-4 (personal communication: Dr Grace Callagy, consultant pathologist in UCHG).

The inflammation grade on biopsies was categorised as normal, mild, moderate or severe in all units. Not all liver biopsies had fibrosis scored numerically. Some were text descriptions. The consultant histopathologists kindly agreed to score these liver biopsies for the purpose of the database. Appendix H includes a table comparing the main liver biopsy scoring systems.

Liver function tests

The units provided reference ranges for the liver function tests (LFT) that allowed us to classify them as abnormally low, normal or abnormally high. We focused on abnormally low results for albumin and abnormally high results for all of the other LFTs for the baseline analysis. Not all units had prothrombin ratio (PTR) reference ranges and PTR/International normalised ratio (INR) tests were not done for the majority of patients (74%). Therefore these results were excluded from the baseline analysis.

Coding of death certificates

Death certificates were collected on deceased patients from the General Registry Office (GRO). This was done by the research nurse, acting on behalf of the hepatology unit. No named data were brought to

HPSC. The cause of death was coded using the World Health Organization (WHO) ICD-10 coding format. Where more than one cause of death was recorded, the underlying cause was selected as the cause of death and this was entered into the database.

The underlying cause was further classified using the following broad categories:

- Death directly caused by liver-related disease
- Death not directly caused by liver-related disease, but liver-disease or hepatitis C listed as a contributing condition on the death certificate
- Death was not liver-related

Death was considered to be directly caused by liver-related disease in the following situations:

If the death certificate mentioned (anywhere except under contributing causes) hepatocellular carcinoma or end-stage liver disease (varices, ascites, liver failure or hepatic encephalopathy)

Or if liver disease was not specified as end-stage (e.g. cirrhosis) but the sequence of causes of death on the certificate suggested death was due to liver disease, e.g. cause 1a: pneumonia, cause 1b: cirrhosis of liver, cause 1c: chronic hepatitis C

Or if liver disease was coded as the underlying and only cause of death.

The classification of all deaths was carried out by a consultant hepatologist and a medical epidemiologist, blinded to the hepatitis C RIBA or PCR status.

This classification is similar to that used by the UK Hepatitis C Register and thus may allow for comparisons to be made in mortality between the two populations.[14]

Long-term medications

Long term medications mentioned in the patient's chart are recorded in the database and were coded using the Anatomical Therapeutic Chemical (ATC) classification system. This is a standardised coding system, controlled by the World Health Organization and is based on the organ or system on which the drug acts.

Data analysis

Data analysis was done using Business Objects, Microsoft Access 9.0, Microsoft Excel 9.0 and Stata/SE version 9.2. Either Pearson's Chi-square or the Wald test, with corresponding probability value (P-value) and 95% confidence intervals, were used to test for differences between odds of a given outcome in logistic regression analysis. Cox regression was used to examine survival since infection with hepatitis C. All statistical tests were 2-tailed.

Chapter 4 Main Findings

Response rates

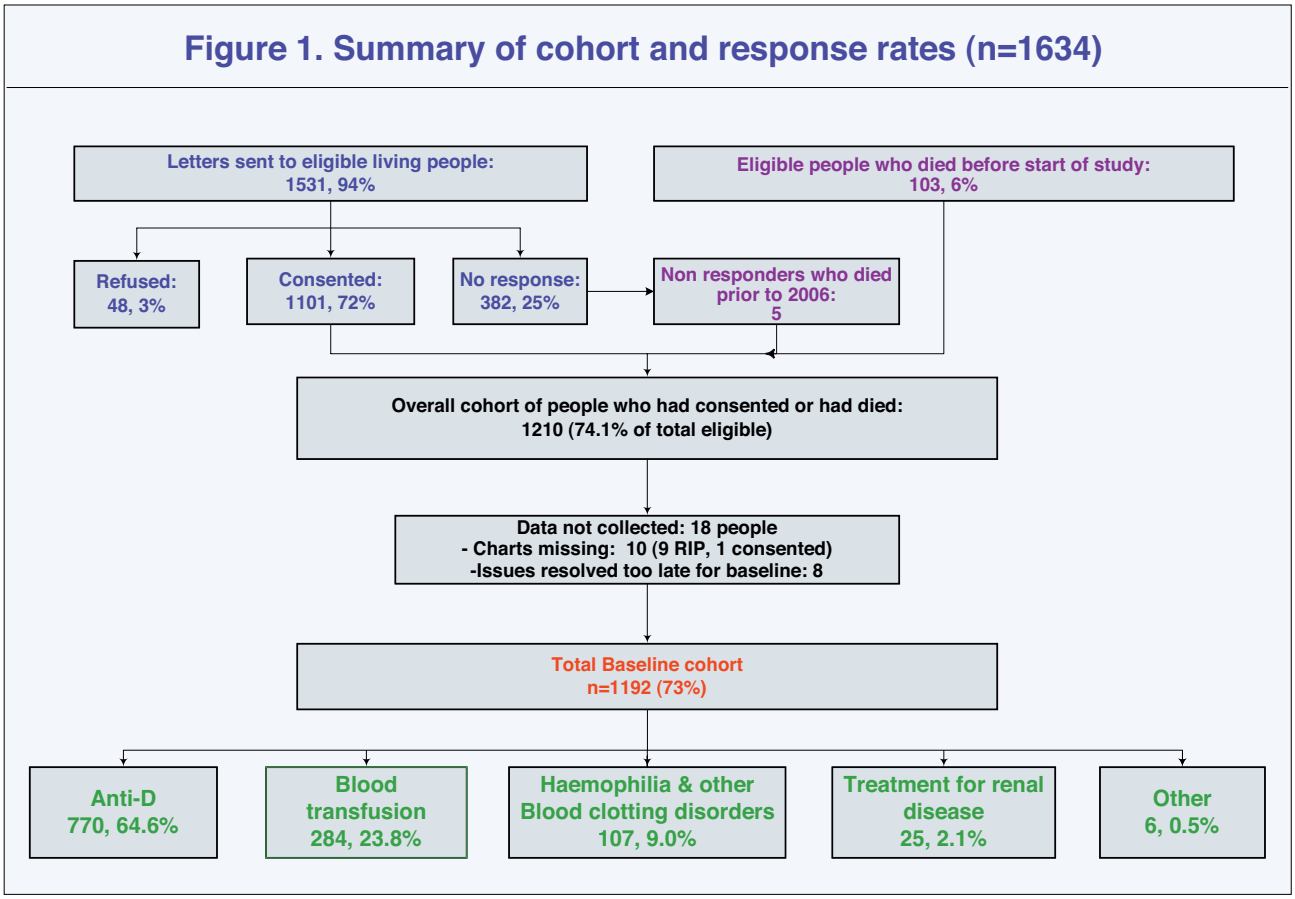
One thousand, six hundred and thirty four (1,634) eligible patients were identified after a process of de-duplication and elimination of ineligible patients from the initial lists prepared by the hepatology units. Of these, 103 patients had died. Letters were sent to the remaining 1,531 patients, inviting them to consent to participate in the database. Of these, 1,101 (72%) consented, 382 (25%) did not respond and 48 (3%) refused to participate (figure 1). Twelve of the patients who consented and five who did not respond have since died and were included in the baseline data.

The overall cohort of patients who consented to participate or had died comprised 1,210 patients. Data were not collected for 18 of these: ten charts were missing (9 deceased patients and 1 live patient) and issues regarding eligibility were resolved too late for the remaining 8 to be included in this round of data collection.

Therefore, the total baseline cohort consisted of 1,192 patients. The most common source of infection was receipt of anti-D immunoglobulin (n=770, 65%), followed by blood transfusion (n=284, 24%), treatment for haemophilia and other blood clotting disorders (n=107, 9%) and treatment for renal (kidney) disease (n=25, 2%).

Six remaining patients are grouped under 'other' for the remainder of this report and are not included in any of the analyses that were done by source of infection in order to avoid reporting data that might allow for the identification of individual patients. This category included patients infected through a state-infected mother or partner.

Figure 1. Summary of cohort and response rates (n=1634)



Representativeness of baseline cohort

The hepatology units provided us with a breakdown of the number of patients who refused or did not respond, by age, sex and source of infection, so that we could check how representative the baseline cohort was of all eligible patients.

The non-participants were found to differ from the participants in relation to age of the patient at the time of recruitment, sex and source of infection. Older age groups were more likely to participate, even after excluding deceased patients. This means that our baseline cohort over-represents older patients, who may be more likely to have other medical conditions and more progressive hepatitis C disease.

With regard to source of infection, blood transfusion patients were more likely to participate in the database, but this difference no longer existed when deceased patients were excluded. Blood clotting disorder patients were significantly less likely to participate compared to the other three groups. Therefore, patients included in the baseline cohort may be less representative of all eligible blood clotting disorder patients compared to the other groups. Females were significantly more likely to participate than males, but it was difficult to separate out the effects of sex and source of infection as all of the anti-D patient group was female and the vast majority of the blood clotting disorder patients were male (table 11)

Table 11. Number of patients and percentage participation in baseline by source of infection

Source of infection	Total baseline participants	Number live (%)	Number RIP (%)	Total eligible for baseline	% participtaion in baseline
Anti-D	770	736 (95.6)	34 (4.4)	1040	74.0
Blood transfusion	284	231 (81.3)	53 (18.7)	360	78.9
Blood clotting disorders	107	94 (87.9)	13 (12.1)	178	60.1
Renal	25	14 (56.0)	11 (44.0)	32	78.1
Other	6	5 (83.3)	1 (16.7)	24	25.0
Total	**1192**	**1080 (90.6)**	**112 (9.4)**	**1634**	**72.9**

Source of infection was not provided for some of the non-participating patients

Description of baseline cohort

Age and sex

Over eighty percent of the cohort was female. This is mainly due to the large female anti-D group, which comprised 65% of the entire cohort. Most of the blood clotting disorder patients were haemophiliacs and this group is 93% male (table 12).

The median age at infection for the baseline cohort was 28 years. However, this varied by source of infection and was lowest for the blood clotting disorder group (13 years) and highest for the blood transfusion group (33 years). The anti-D cohort were all infected between the ages of 16 and 44 years. There was a greater spread of age at infection for the other sources, with ages ranging from 0 to 77 years for the blood transfusion group. Age at infection was assigned according to the assumptions described in the methods section and is likely to be less accurate for the blood clotting disorder and renal patients (table 12, figure 2).

Table 12. Number of patients by sex and median age at infection for baseline cohort by source of infection

Source of infection	Number of patients (%)			Median age at infection (range)		
	Male	Female	All	Male	Female	All
Anti-D	0	770 (100)	770		28 (16-44)	28
Blood transfusion	111 (39.1)	173 (60.9)	284	32 (0-71)	34 (0-77)	33
Blood clotting disorders	99 (92.5)	8 (7.5)	107	13 (0-53)	21 (5-32)	13
Renal	15 (60.0)	10 (40.0)	25	29 (8-67)	28 (16-62)	29
All	**225 (19.0)**	**961 (81.0)**	**1186**	**22**	**28**	**28**

*"Other sources" of infection are excluded from this table (n=6)

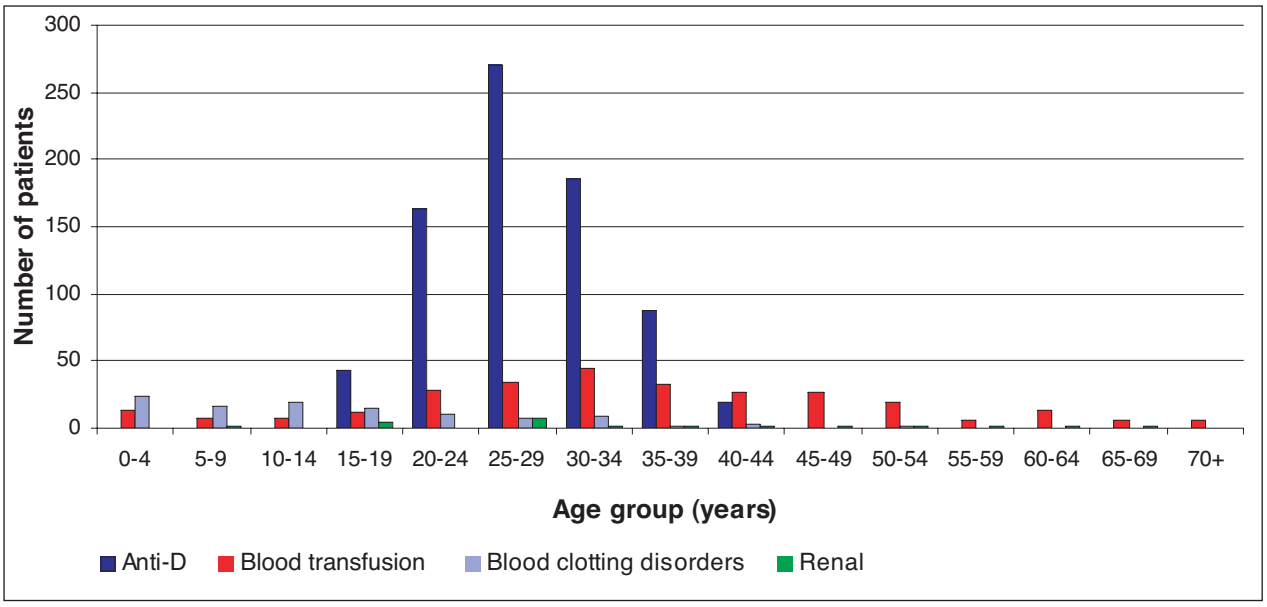


Figure 2. Distribution of age at infection by source of infection

At the end of 2005, the median age for living participants was 55 years (range: 14-94). The median ages by source of infection were: 55 (31-72) for the anti-D group, 58 (14-94) for the blood transfusion group, 42 (20-78) for the blood clotting disorder group and 52 (25-67) for the renal group (figure 3).

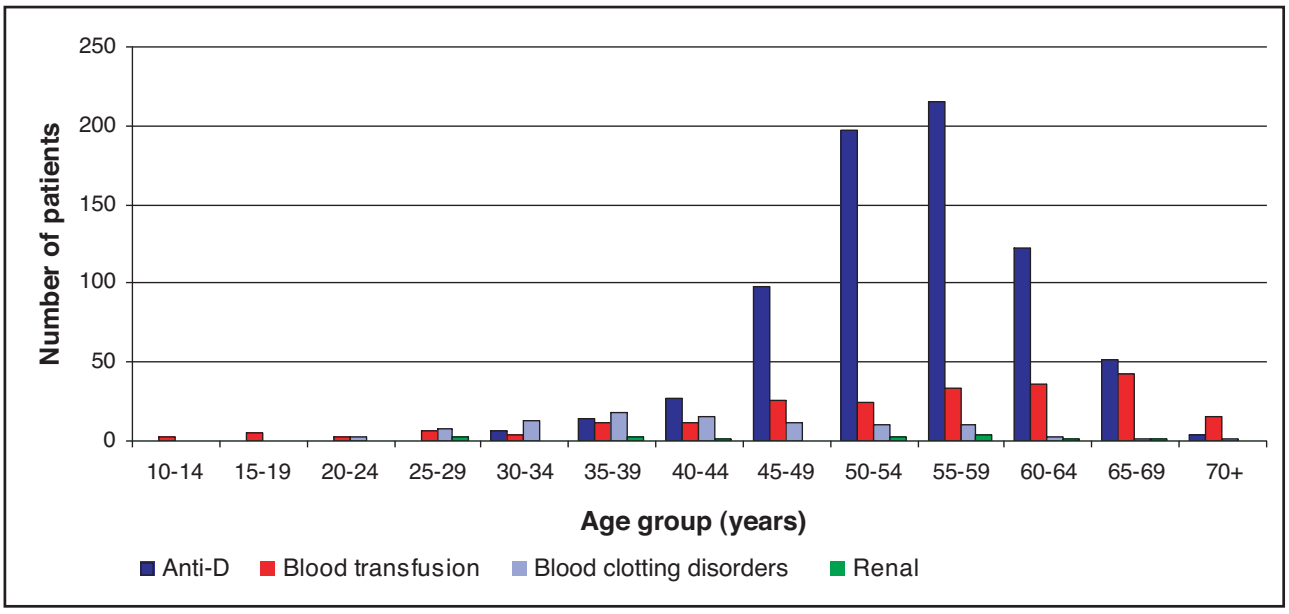


Figure 3. Distribution of age at the end of 2005 by source of infection (for living patients only)

Body mass index (BMI)

Weight and height were recorded in the medical charts for only 171 patients. Therefore, it was not possible to include BMI in any further analyses. Where weight and height were available, 2% of patients were underweight, 38% were of normal weight, 37% were overweight and 22% were obese.

Pregnancies and live births

The vast majority of women had at least one child (92%). The median number of live births for women who had at least one child was 4 (range: 1-15).

County of residence

The county of residence of the participants is shown on the map below. This information may be useful for service planning.

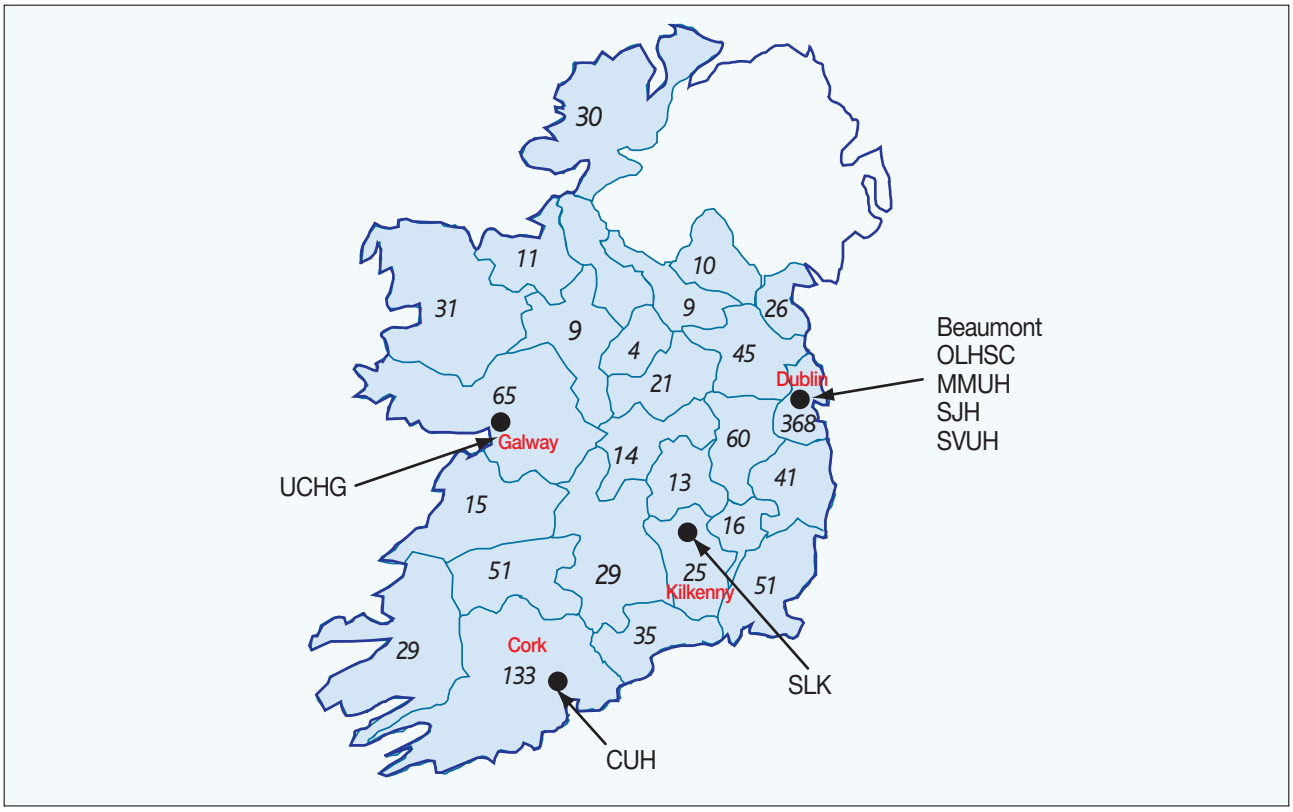


Figure 4. Number of patients resident in each county and location of the 8 hepatology units (county of residence not known for 42 patients and was outside of the Republic of Ireland for 4)

Hepatology unit abbreviations

OLHSC	Our Lady's Children's Hospital, Crumlin
MMUH	Mater Misericordiae Universtiy Hospital
SJH	St. James's Hospital
SVUH	St. Vincent's University Hospital
SLK	St. Luke's Hospital, Kilkenny
CUH	Cork University Hospital
UCHG	University College Hospital Galway

Year of infection

Anti-D

Background information

Hepatitis C infection due to receipt of contaminated anti-D has been largely traced to two donors who had undergone plasma exchange and received donated blood or blood products themselves. The first donor was the source of 16 batches of anti-D distributed between 1977 and 1979. Eight of these batches later tested positive for hepatitis C genotype 1b.[15]

The second donor was the source of 46 batches of anti-D, of which 43 were issued. Twenty later tested positive for hepatitis C and infectivity could not be ruled out for the remaining twenty three. In this case, the hepatitis C genotype was 3a. These batches were issued between March 1991 and February 1994.[15] *The 1991-94 batches of anti-D were of lower infectivity than the 1977-79 batches, probably due to the relatively low level of hepatitis C RNA in the plasma from that donor.*[16]

Ninety three percent of the baseline anti-D cohort were infected in an outbreak year (1977-1979 or 1991-1994) and where genotyping was carried out, had the hepatitis C genotype associated with the outbreak period. However, 49 anti-D patients were infected outside the outbreak periods and 6 patients who were infected in an outbreak year did not have the genotype associated with that outbreak. Some of these had other potential sources of infection, so their source may have been wrongly assigned (table 13).

Over 80% (n=650, 84%) of our participating anti-D cohort were assigned a year of infection between 1977 and 1979. Where these patients were genotyped (n=344), all were genotype 1. Subtyping was carried out for 158, and all except 1 were type 1b. Nine percent (n=71) of anti-D patients had an assigned year of infection between 1991 and 1994. Genotyping was done for 40 patients infected in this period, and 35 (88%) were genotype 3. Subtyping was only carried out for four patients, all of whom were type 3a (figure 5).

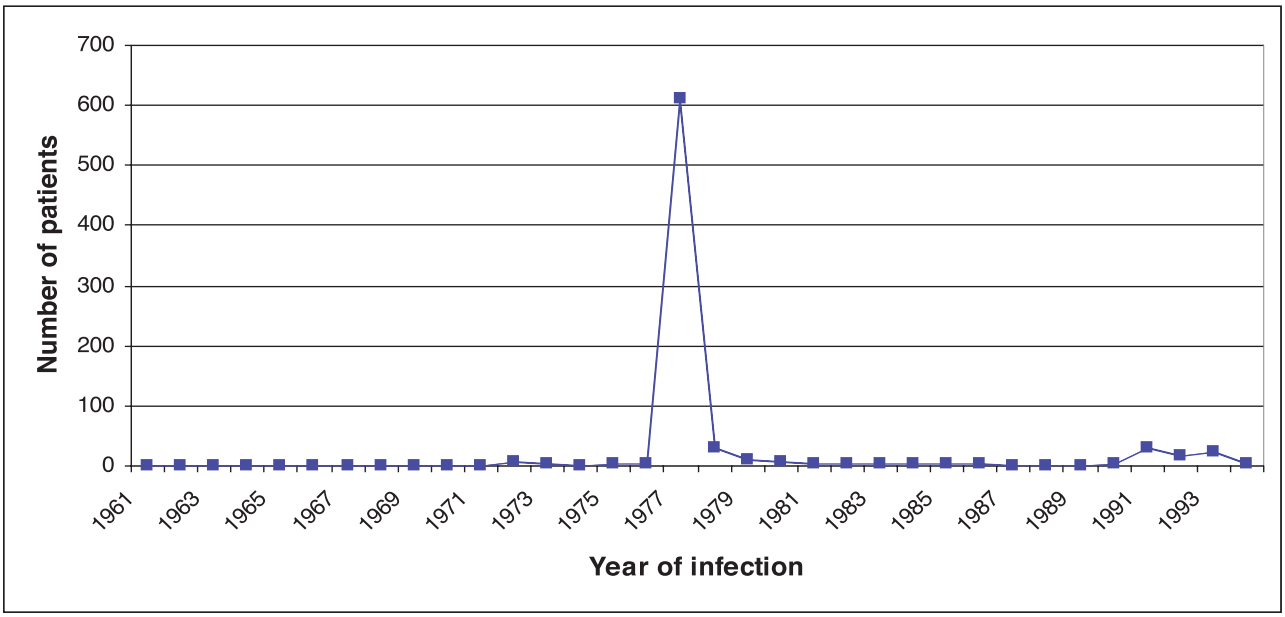


Figure 5. Distribution of year of infection for anti-D patients
(See assumptions in chapter 3)

Table 13. Years of infection for anti-D patients whose assigned year was outside of an outbreak period

1961	1964	1969	1970	1971	1972	1973	1975	1976	1980	1981	1982	1983	1984	1985	1986	1988	1989	1990
1	1	1	1	1	5	2	2	4	7	3	4	3	3	2	3	1	1	4

We attempted to collect data on anti-D batch numbers, but the batch number received was only recorded in the medical charts of 13% of anti-D patients. It may be useful for the hepatology units to link with the IBTS in the future to obtain more complete data.

Blood transfusion

Background information

The IBTS began screening blood for hepatitis C on Oct 1st 1991. Prior to this, screening questionnaires were used to detect potential donors with risk factors for viral infections. A targeted lookback programe was introduced for transfusion recipients in January 1995. Its starting point was tracing recipients of past donations from donors who were later identified as being infected with hepatitis C. A more generalised "optional" screening programme was introduced in September 1995, which offered free screening to anyone who had received blood or blood products in Ireland prior to October 1991.[3]

The peak period of infection for blood transfusion recipients was between 1977 and 1991, during which 78% of the participating blood transfusion cohort became infected. We are reasonably confident regarding the year of infection assigned to 65% of blood transfusion patients as they either had only one transfusion or they had received blood from a donor who was later identified as being infected with hepatitis C. The remaining patients had multiple blood transfusions and/or other blood exposures. For these patients, the year of the earliest transfusion was taken as the year of infection. As a result, our data may be biased towards earlier years of infection (figure 6).

A small number of people had transfusions after the introduction of screened blood (indicated in grey on figure 6). It is highly unlikely that infection was due to screened blood as the incidence of transfusion-transmitted hepatitis C after the introduction of screening was of the order of 1 in 100,000 or less (personal

communication from Dr Emer Lawlor, IBTS 2007). We hope to further clarify the details of these cases in future reports.

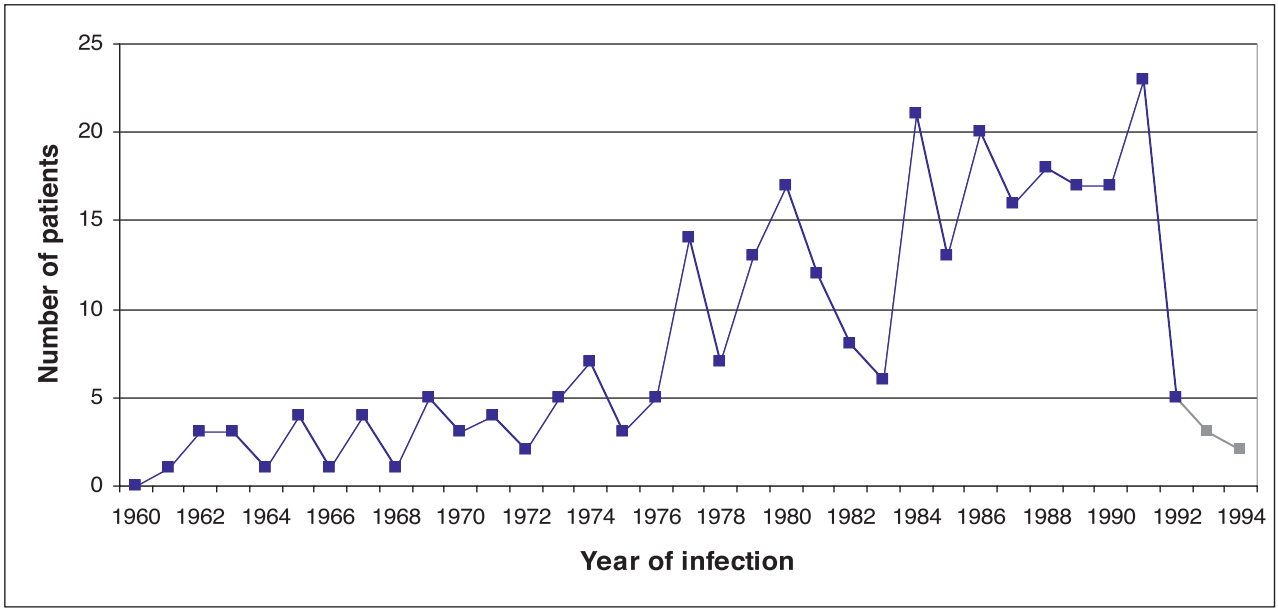


Figure 6. Distribution of year of infection for blood transfusion patients
(See assumptions in chapter 3)

Treatment for blood clotting disorders

Background information

Blood clotting disorders were originally treated using whole blood or plasma. The IBTS (formerly the BTSB) began producing cryoprecipitate with factor VIII in 1967 and fractionated factor IX in 1972. Commercially fractionated factor VIII and factor IX became available in Ireland from 1974 and 1977 onwards, respectively. Such preparations were manufactured from large pools of plasma from paid donors.[17] From 1984 to 1989, the IBTS entered into an arrangement with a number of companies for custom fractionation – plasma collected from voluntary Irish donors was supplied to commercial companies who fractionated factor VIII and IX from it and then supplied those products to the IBTS for use in Ireland. From 1990 onwards, the product was solvent detergent treated. This process inactivates hepatitis C, hepatitis B and HIV viruses. There is no evidence that hepatitis C has ever been transmitted by solvent detergent treated products in Europe or the US (personal communication from Dr Emer Lawlor, IBTS 2007).

The year of hepatitis C infection was not clear from the medical records of any of the blood clotting disorder patients as they had been receiving potentially infectious blood clotting factors on an ongoing basis over long periods of time. Year of infection was therefore assigned as the year the patient first received blood clotting factor. As a result, our data is biased towards earlier years of infection. In addition, 41% of blood clotting disorder patients had received blood or other blood products in addition to clotting factors. This was discussed with their consultant hepatologist and it was decided that infection was most likely to be due to clotting factors and assigned as such.

The peak years for hepatitis C infection for blood clotting disorder patients were 1974 (n=22, 21%) and 1982 (n=10, 9%). The year of infection assigned to one patient was after 1991 (indicated in grey in figure 7). This was because notes were missing from the medical chart and the earliest date factor was received was not available. We hope to clarify the infection details for this patient during follow up data collection (figure 7).

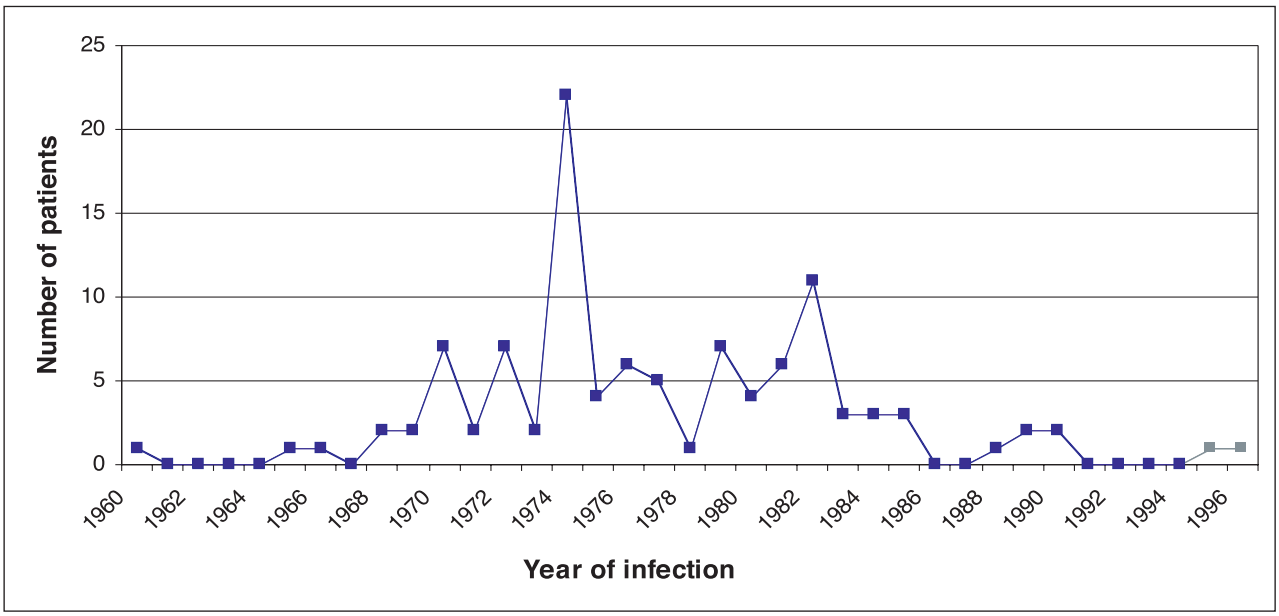


Figure 7. Distribution of year of infection for blood clotting disorder patients (See assumptions in chapter 3)

Treatment for renal disease

The year of infection was not known for any of the renal patients as most had been on dialysis for extended periods of time and 96% (n=24) had also received one or more blood transfusions and/or kidney transplants. In these cases, the year dialysis was started or the date of the first blood transfusion (whichever was earlier) was used as an estimate of the year of infection. This is likely to have biased the distribution of cases towards earlier years of infection and may have concealed actual trends. Based on the assigned year of infection, cases of hepatitis C in renal patients were spread over time. The year of infection assigned to four patients was after 1991. One had only started dialysis in 2000 and the remaining three had previously tested negative for hepatitis C. Thus, the assigned dates of infection for these patients are likely to be close to their real dates of infection (figure 8). As outlined previously, any post-1991 infections in renal patients were highly unlikely to be due to blood transfusions.

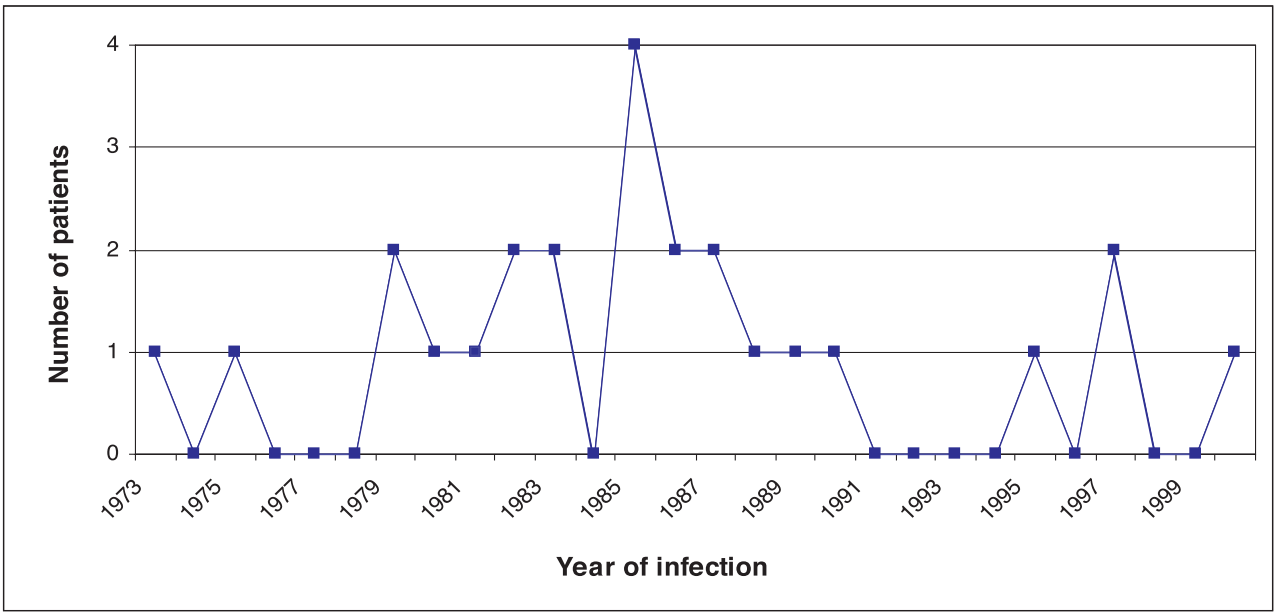


Figure 8. Distribution of year of infection for renal patients (See assumptions in chapter 3)

Hepatitis C antibody and polymerase chain reaction (PCR) results

Sixty three percent of patients (n=746) tested hepatitis C PCR positive at some stage. A further one hundred and ninety one patients (16%) tested RIBA positive but were not PCR positive. These patients cleared the virus prior to diagnosis but had confirmatory antibody evidence of infection and are considered confirmed positive for hepatitis C (see glossary for case definitions) (table 14).

Table 14. Hepatitis C antibody and PCR results for the baseline cohort

Antibody and PCR results	Number of patients	% of patients
Ever HCV PCR positive	746	62.6
HCV RIBA positive	191	16.0
HCV EIA positive, RIBA indeterminate	90	7.6
HCV EIA positive only	28	2.3
HCV EIA weak positive, RIBA indeterminate	58	4.9
HCV RIBA indeterminate only	59	4.9
HCV EIA weak positive only	18	1.5
No positive test results in chart but eligible*	2	0.2
Total	**1192**	**100**

*Notes missing from charts, but hepatology units indicated that patients were antibody positive

Two hundred and fifty three patients (n=21%) tested hepatitis C EIA positive, hepatitis C RIBA indeterminate or EIA weak positive and had no other positive test results. RIBA is a confirmatory test and either a positive RIBA result or a positive PCR test are usually necessary to confirm a diagnosis of hepatitis C.[18] However, testing took place many years after infection for most patients. Thus it is likely that some may have been infected, cleared the virus and antibody may have declined below detectable levels.[18] Other patients may have had a positive EIA screening test but did not return for a confirmatory test. Therefore, it was decided to include patients with only RIBA indeterminate and EIA positive or weak positive results in the database. However, some analyses were done on confirmed cases only (see glossary for case definitions).

We investigated the two patients who appear to have no positive antibody or PCR test results. The hepatology units have confirmed that these patients are eligible and had positive antibody results, but some results are missing from their charts and are therefore not available for the baseline analysis.

Most of the subsequent analysis is presented separately for patients who tested PCR positive at some stage and patients with no positive PCR results in their charts. Most of the patients who tested PCR positive and have since cleared the virus, did so relatively recently and in most cases this was due to treatment. The median duration of infection at last positive PCR test for patients who ever tested PCR positive was 26 years (range: 1-45). This is very similar to their median duration of infection at last visit to the hepatology unit (27 years, range: 1-45). We have no information on the timing of viral clearance for patients with no positive PCR results in their charts, but the majority of patients who clear the virus without treatment do so within the first year of infection.[19]

The proportion of patients who ever tested hepatitis C PCR positive varied significantly by source of infection, with the anti-D group having the lowest proportion of patients ever testing PCR positive (table 15). When only patients who tested PCR or RIBA positive (confirmed positive) were considered, blood transfusion and renal patients remained more likely to have ever tested PCR positive than anti-D patients. Males were significantly more likely to have ever tested PCR positive compared to females. Female gender has been associated with higher rates of viral clearance in other studies, so this may partially explain the higher viral clearance rate in the anti-D group compared to the other groups [20] (appendix J: table 47). PCR status did not vary significantly by age at infection.

Table 15. Hepatitis C antibody and PCR results by source of infection

Source of infection	PCR positive (%)*	RIBA positive but not PCR positive (%)*	Not confirmed positive (%)	Total	Last PCR test positive (%)†
Anti-D	409 (53.1)	144 (18.7)	217 (28.2)	770	346 (44.9)
Blood transfusion	225 (79.2)	27 (9.5)	32 (11.3)	284	169 (59.5)
Blood clotting disorders	85 (79.4)	19 (17.8)	3 (2.8)	107	57 (53.3)
Renal	24 (96.0)	0	1 (4.0)	25	22 (88.0)
Total	**743 (62.6)**	**190 (16.0)**	**253 (21.3)**	**1186**	**594 (50.1)**

*Patients who ever tested PCR or RIBA positive are considered confirmed positive

†The last PCR result is not a definitive indicator of current status as the PCR status of patients on treatment may fluctuate

The overall viral clearance rate for our cohort was 37% considering all patients and 20% if only patients who were confirmed positive for hepatitis C are considered. A systematic review of longitudinal studies that reported spontaneous viral clearance following acute hepatitis C infection, found a viral clearance rate of 26 percent (95% confidence interval 22%-29%) overall and a rate of 18% (95% confidence interval 13%-24%) in post-transfusion hepatitis studies.[20]

The median number of PCR tests recorded in the medical charts is shown in table 16. Although PCR levels can fluctuate, most patients who never had a PCR positive result had many PCR tests done so it is unlikely that the presence of circulating virus was missed. Only six patients have no record of PCR tests in their charts.

Table 16. Median number of PCR tests done, by PCR and treatment status

PCR and treatment status	Median	Range
Patients ever PCR positive and treated	18	1-62
Patients ever PCR positive and not treated	9	1-22
Patients with no positive PCR results in chart	6	0-32

We have recorded all PCR results for our patient cohort. Therefore, for patients who ever tested PCR positive and subsequently clear the virus, it is possible to estimate how long they have had circulating virus and relate this to disease progression. These data will become more interesting in the future as we follow the natural history of this cohort. All viral load results, and full RIBA banding patterns for the first and last test have been recorded and are available for analysis.

Genotype

The vast majority of patients who ever tested hepatitis C PCR positive had genotype testing done (n=709, 95%). The distribution of genotypes varied by source of infection (table 17, figure 9).

Of anti-D patients genotyped, 90% were genotype 1 and 10% were genotype 3. The proportion of genotype 1 patients was lower for the remaining groups; 58% of blood transfusion patients, 63% of blood clotting disorder patients and 50% of renal patients Where subtyping of genotype 1 patients was carried out (n=211) 91% were type 1b (table 17, figure 9).

Table 17. Number and percentage of patients with each hepatitis C genotype by source of infection

Source of infection	Hepatitis C genotype					Total
	1	2	3	4	5	
Anti-D	354 (89.8)	1 (0.3)	39 (9.9)	0	0	394
Blood transfusion	125 (57.6)	25 (11.5)	66 (30.4)	0	1 (0.5)	217
Blood clotting disorders	47 (62.7)	8 (10.7)	17 (22.7)	2 (2.7)	1 (1.3)	75
Renal	10 (50.0)	1 (5.0)	9 (45.0)	0	0	20
Total	**536 (75.9)**	**35 (5.0)**	**131 (18.6)**	**2 (0.3)**	**2 (0.3)**	**706**

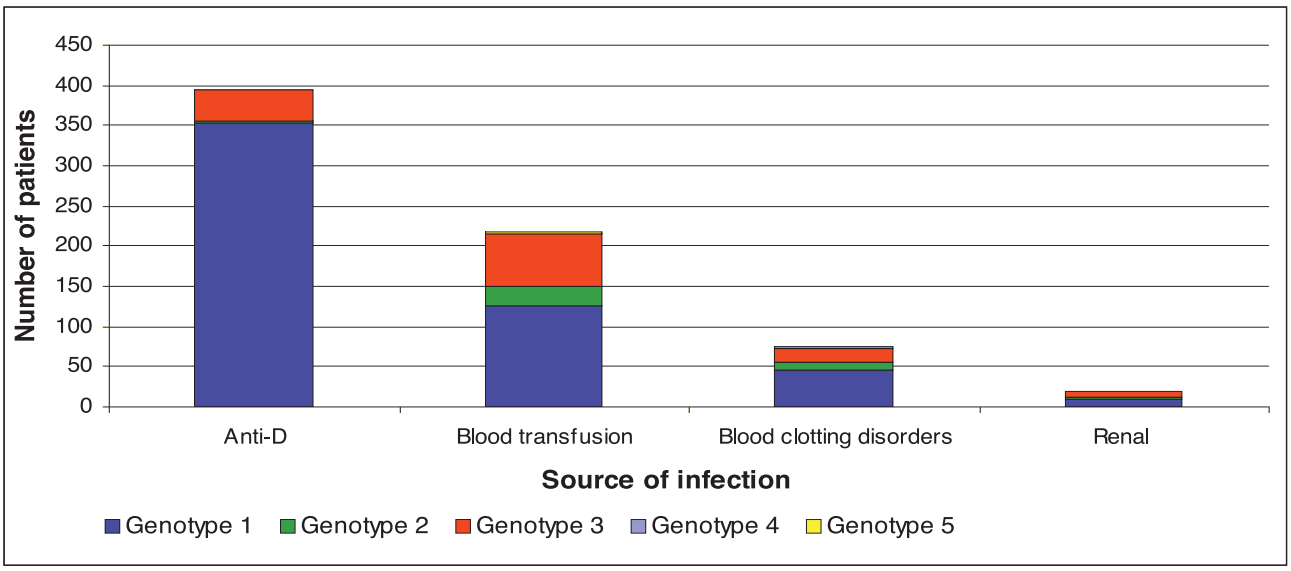


Figure 9. Distribution of hepatitis C genotypes by source of infection

The proportion of genotype 1 patients in our cohort was higher than that found in the general population in a study done by the National Virus Reference Laboratory between 1994 and 1999. They carried out genotype testing on over 2,800 samples and found that 59% were genotype 1, 37% were genotype 3 and 3% were genotype 2. This disparity in findings was due to the large genotype 1 1977-1979 anti-D outbreak. [21]

The distribution of genotypes by year of infection is shown in figures 10 and 11. The genotype 1 peak between 1977 and 1979 is mainly attributable to patients affected by the first anti-D outbreak. The genotype 3 peak between 1990 and 1994 comprises mostly anti-D and blood transfusion patients.

Genotype determinations influence treatment decisions as the success rate of anti-viral treatment is higher for genotypes other than type 1.[7] There is little evidence that genotype affects the risk of progression of liver disease.[7,9]

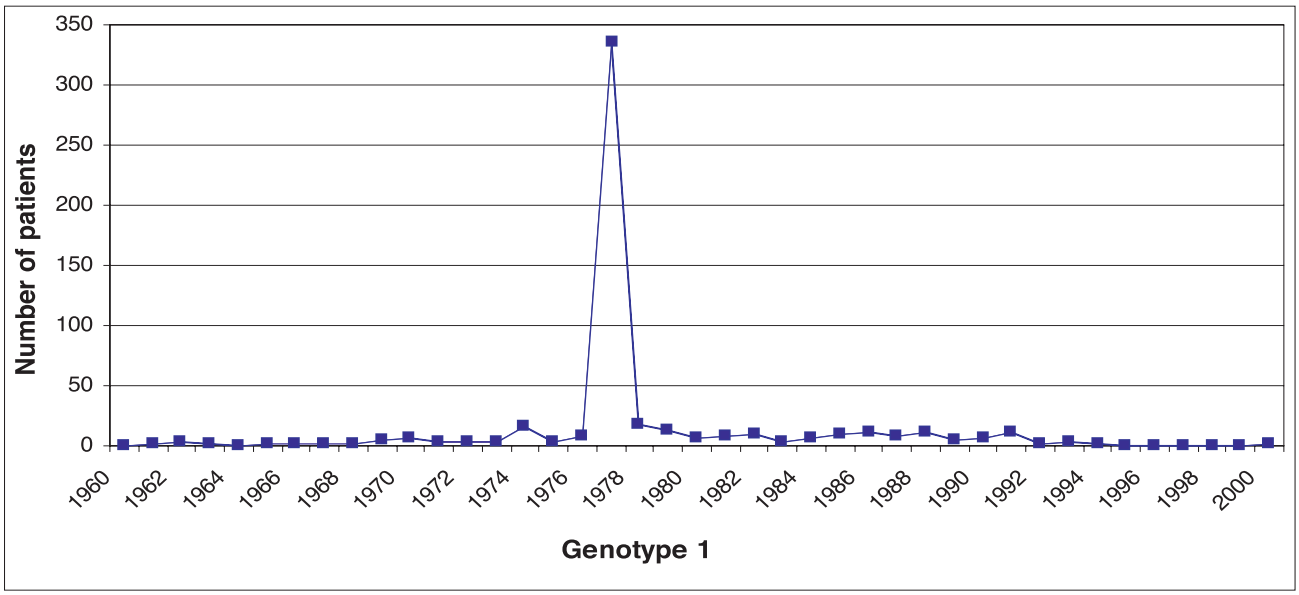


Figure 10. Distribution of hepatitis C genotype 1 by year of infection

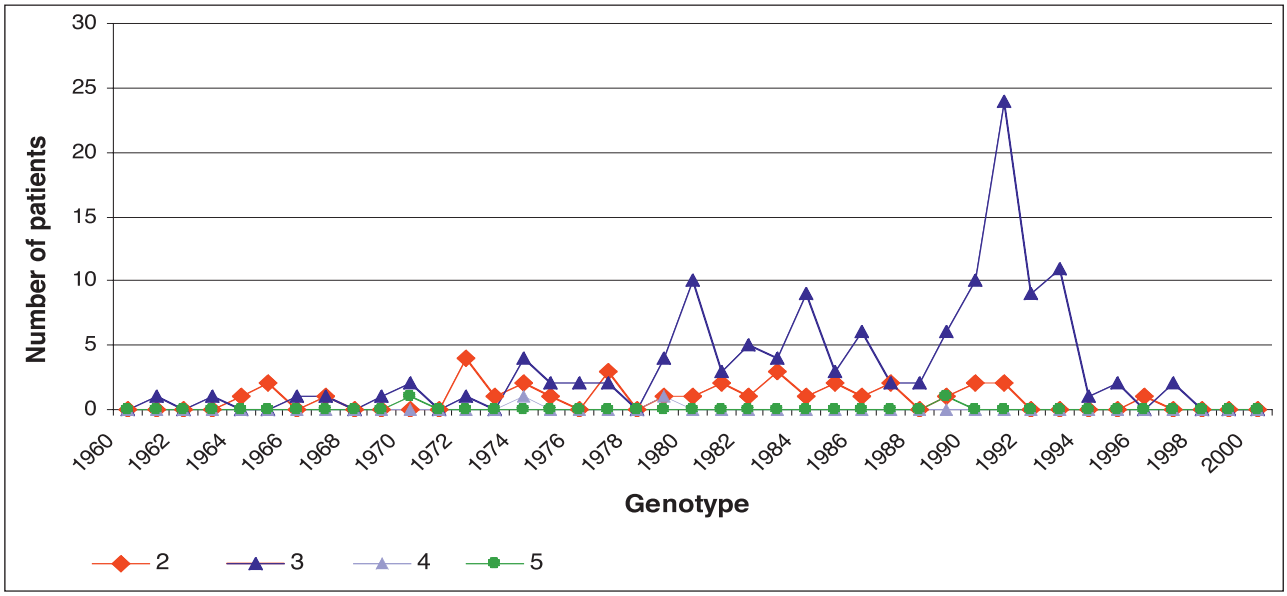


Figure 11. Distribution of hepatitis C genotypes 2, 3, 4 and 5 by year of infection

Attendance at the hepatology units

The distribution of the year of first visit to the hepatology unit is shown in figure 12. The majority of patients first attended between 1994 and 1996.

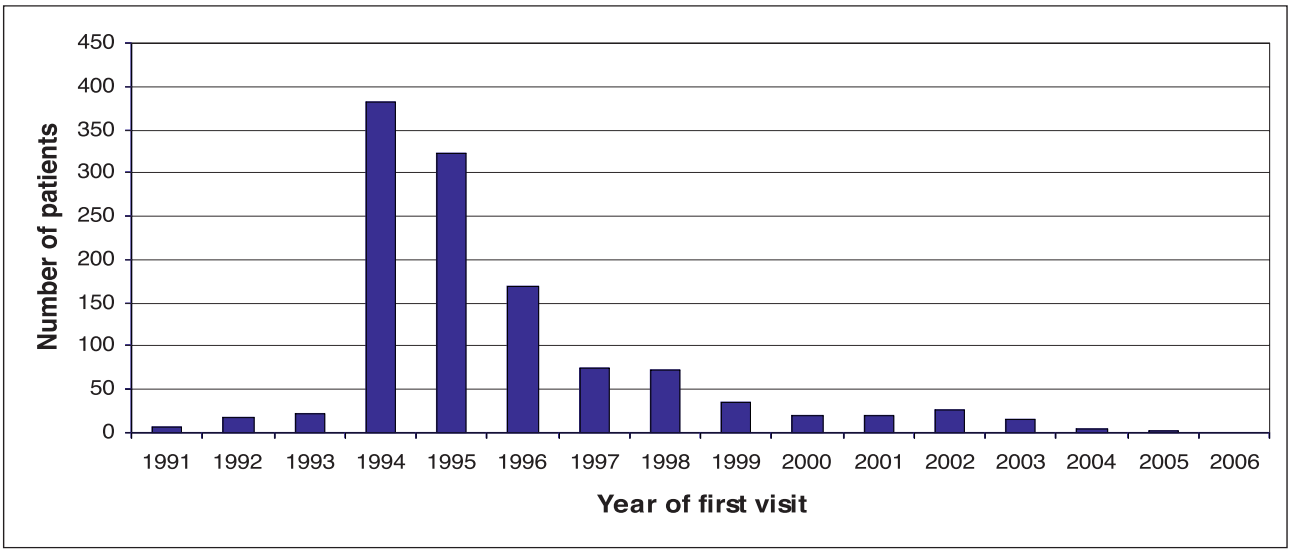


Figure 12. Distribution of year of first visit to the hepatology unit

Frequency of attendance at the hepatology units is likely to vary depending on the patient's clinical status and practices within individual units. Data collection was carried out throughout 2005 and 2006, and data for an individual reflects that contained in their charts at the time of data collection.

As would be expected, PCR positive patients were more likely to have attended the hepatology unit recently. Eighty seven percent of living patients who had ever tested hepatitis C PCR positive had attended their hepatology unit in the year prior to data collection, compared to 56% of patients with no positive PCR results in their charts (figure 13). Eighty nine percent of deceased patients who had tested PCR positive and 61% of those who had not tested PCR positive, attended their hepatology unit within two years of their death (figure 14).

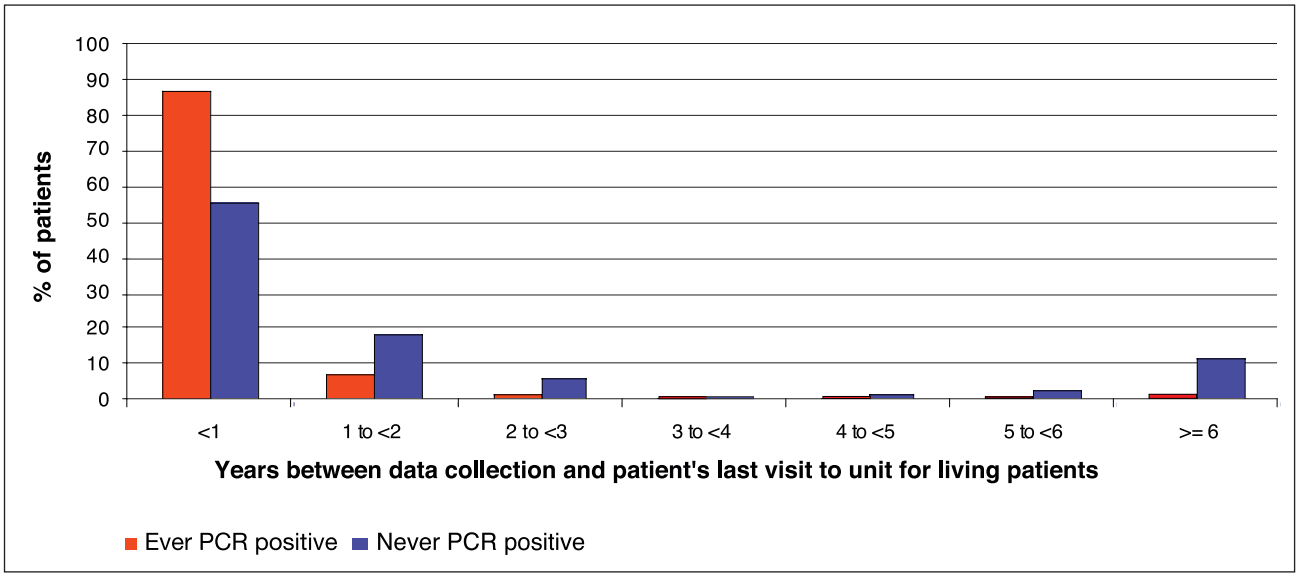


Figure 13. Distribution of years between data collection and last visit to the hepatology unit by PCR status, for living patients

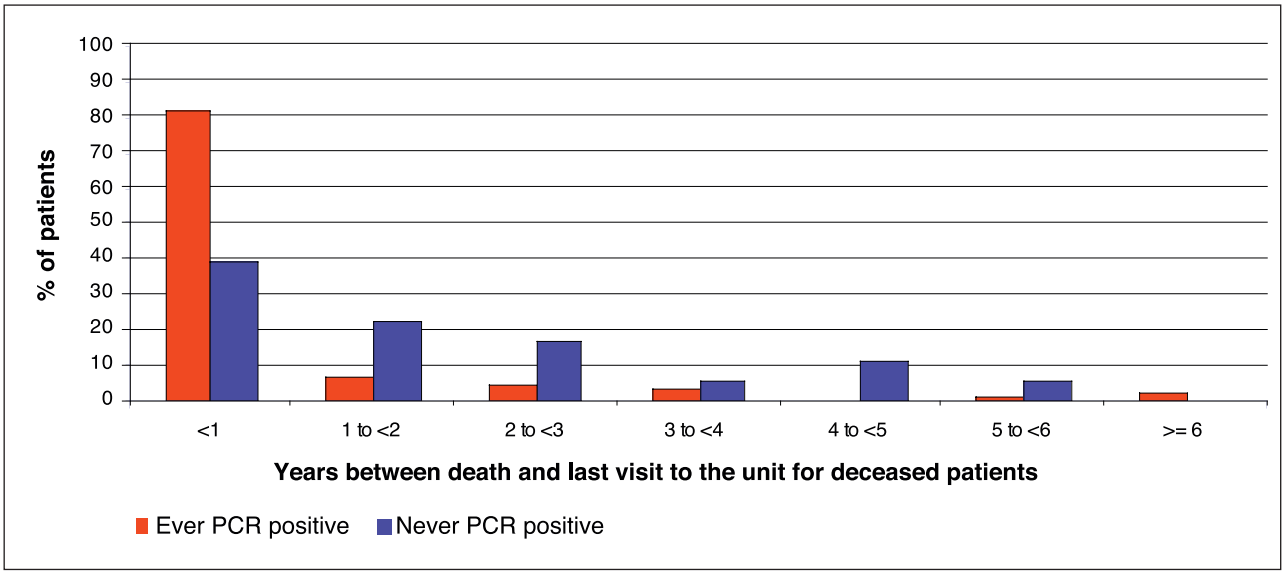


Figure 14. Distribution of years between death and last visit to the hepatology unit by PCR status, for deceased patients

Duration of infection

The duration of infection at last visit to the hepatology units is the period for which we have follow up data. The median duration of infection for the baseline cohort was 27 years. Given that the median time from infection to cirrhosis in the international literature is estimated to be 30 years, this is an important time for follow up of the cohort in terms of progression of disease.[6]

Seventy six percent of our baseline cohort was infected for 20 years or more, and 8% were infected for 30 years or more, by the time of their last visit to the hepatology unit. The duration of infection was particularly long for anti-D and blood clotting disorder patients, with 87% of anti-D patients, and 81% of blood clotting disorder patients, infected for 20 years or more. However, the dates of infection for many of the blood clotting disorder and renal patients, and for some of the blood transfusion patients, were estimated dates based on the assumptions previously described, and the actual duration of infection may be shorter than presented here for these groups (table 18, figure 15).

Table 18. Median duration of infection at last visit to hepatology unit

Source of infection	Median duration of infection at last visit in yrs (range)
Anti-D	27 (3-42)
Blood transfusion	20 (1-44)
Blood clotting disorders	28 (10-45)
Renal	17 (1-32)
Overall median	**27 (1-45)**

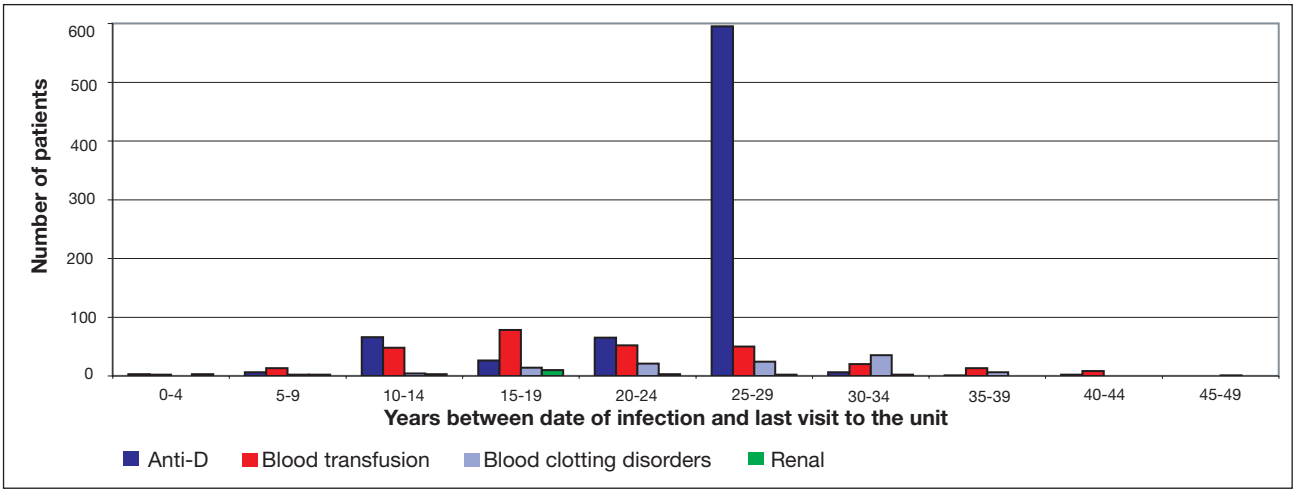


Figure 15. Distribution of years between infection and last visit to the hepatology unit by source of infection

Known risk factors for hepatitis C infection other than blood or blood products

Fifty one patients (4% of cohort) had one or more known risk factors for hepatitis C infection other than the blood/blood products they had received. The most common risk factors recorded were tattooing/ acupuncture/needlestick injuries (n=24, 2%), current or former injecting drug use (n=19, 2%) and having a partner with hepatitis C (n=5, 0.4%).

Alcohol and smoking

Alcohol

The medical charts of 1,046 patients (88% of cohort) had information on alcohol intake at the first visit to the hepatology units. The recommended limits for low-risk alcohol consumption in Ireland are 14 units or less a week for women and 21 units or less for men.[22]

At first visit to the unit, 96% of anti-D patients and 93% of renal patients, whose charts contained information on alcohol intake, were either non-drinkers or consumed alcohol within the recommended limits. The proportion of patients who consumed alcohol in excess of recommended limits was higher for blood transfusion (11%) and blood clotting disorder patients (34%). However, this may be explained by the higher proportion of males in these groups rather than factors relating to source of infection (figure 16).

Data on alcohol intake were less complete at last visit to the unit, with alcohol intake noted for only 200 patients (17%). It would be very interesting to look at how alcohol intake has changed over time, but the baseline data were not complete enough to be representative (figure 17).

Excessive use of alcohol or alcoholic liver disease was also mentioned in the charts of some patients. Combining this information with a record of alcohol intake above the recommended limits at any visit to the unit, 28% of males (n=63) and 6% of females (n=55) had indicators of excess alcohol consumption in their medical records (table 19, appendix J: table 48). Alcohol consumption over the recommended limits did not vary by age at infection, age at diagnosis or age at last visit, after taking sex into account.

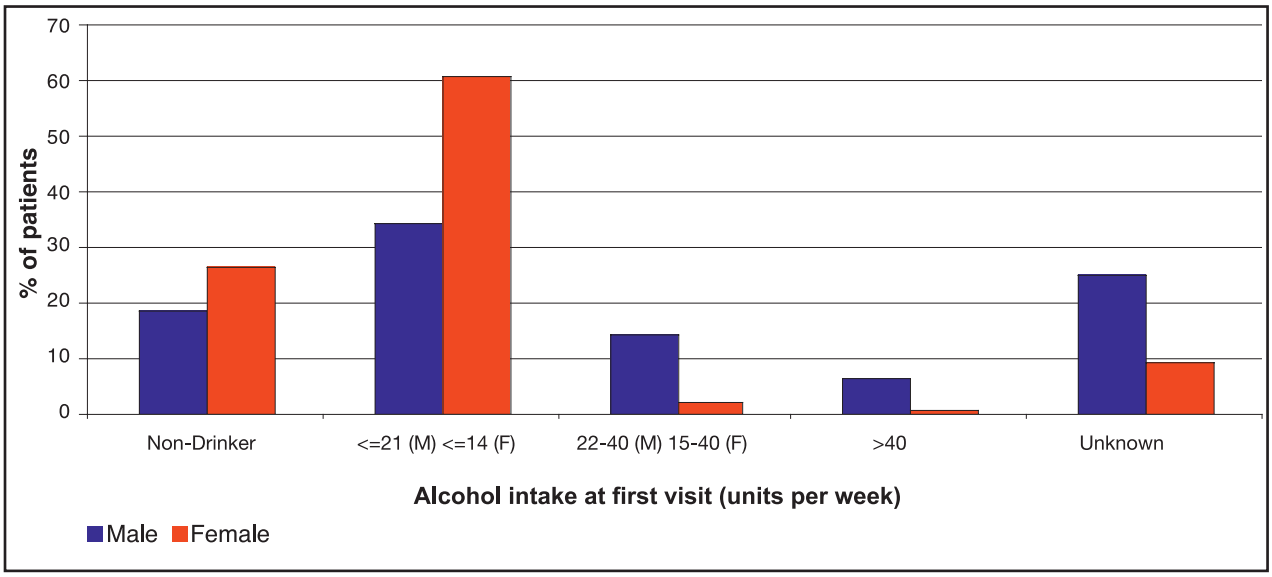


Figure 16. Alcohol intake reported at first visit to the hepatology unit by sex

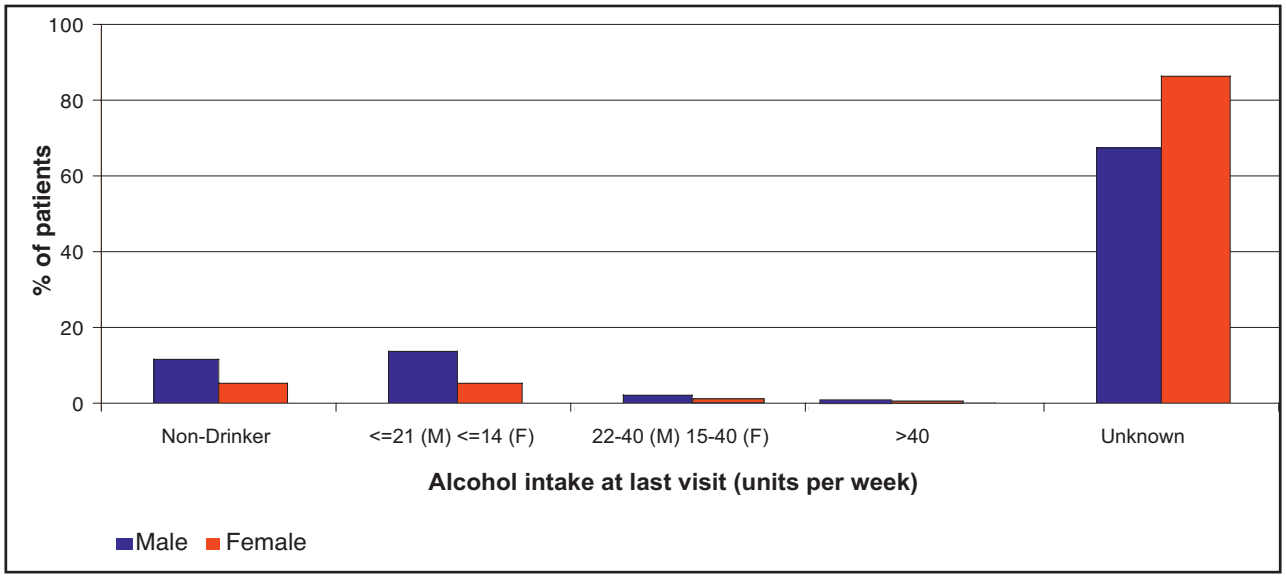


Figure 17. Alcohol intake reported at last visit to the hepatology unit by sex

Table 19. Indicators of alcohol consumption in excess of recommended limits in medical chart by source of infection

Source of infection	Number of patients with indicators of alcohol excess	% of patients
Anti-D	42	5.5
Blood transfusion	42	14.8
Blood clotting disorders	32	29.9
Renal	1	4.0
Total	**117**	**9.9**

Patients with no information about alcohol intake in their charts were included in the denominator when calculating percentages

These figures for excessive alcohol consumption can be compared to those in the general population. The National Lifestyle Survey (SLAN) found that 30% of males and 22% of females consume over the recommended upper limit of 21 and 14 standard drinks respectively, with higher levels in the younger age group.[23] These results need to be placed in the context of a recent study showing that Ireland had the highest reported consumption per drinker and the highest level of binge drinking in comparison to adults in the six other European countries studied.[22]

However, recommended limits for alcohol consumption for the general population may not be appropriate to people with existing liver disease such as chronic hepatitis C. Alcohol consumption is clearly associated

with the rate of progression to fibrosis in hepatitis C infection.[6,7,24] A meta-analysis of published papers on the influence of alcohol on the progression of hepatitis C infection concluded that the evidence overwhelmingly shows a worsened outcome for those with chronic hepatitis C and concurrent alcohol use. Studies varied widely in their definition of significant alcohol intake, and so the true threshold above which alcohol accelerates hepatitis C disease progression remains uncertain. The authors recommend that alcohol consumption should be minimised as much as possible in those who have chronic hepatitis C until a safe threshold is more definitively determined.[25]

Past alcohol consumption may also have a negative impact on treatment response rates in patients with chronic hepatitis C. A recent US study estimated lifetime alcohol consumption in a group of treatment naïve hepatitis C patients and demonstrated that median daily alcohol use >30 g/day was associated with failure to respond to treatment using pegylated interferon and ribavirin.[26]

Smoking

The medical charts of 1,031 patients (86% of cohort) had information on smoking at first visit to the units. Smoking data were less complete at last visit to the unit, with smoking status noted for only 194 patients (16%).

Smoking status and the number of cigarettes smoked per day varied by sex, with males significantly more likely to smoke than females and also more likely to smoke higher numbers of cigarettes per day (figure 18).

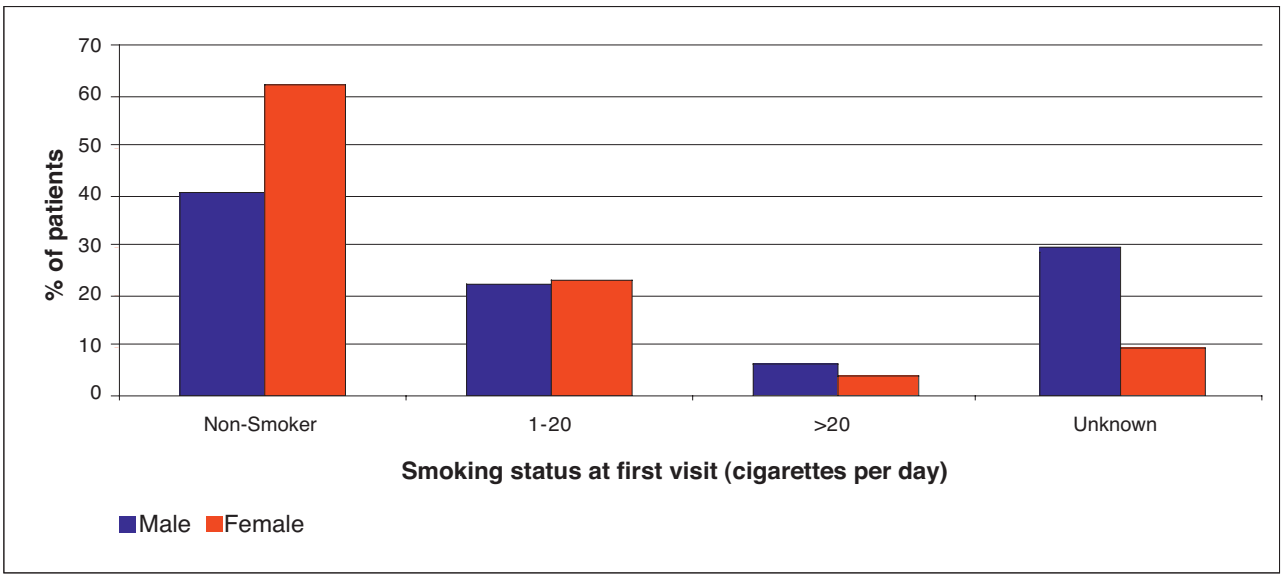


Figure 18. Smoking status reported at first visit to the hepatology unit by sex

Other viral infections

Thirty seven patients (3%) had viral infections other than hepatitis C. The most significant viral infection was HIV. Thirty one blood clotting disorder patients (29%) were co-infected with HIV. This proportion was similar to that found for the entire hepatitis C-infected blood clotting disorder cohort described in the Lindsay report (32%)[17]. Co-infection with HIV has been shown to accelerate progression of hepatitis C infection.[27]

A total of six patients were recorded as positive for hepatitis B surface antigen and two patients tested positive for hepatitis G.

Signs of liver disease

One hundred and fourteen patients (10%) had one or more signs of liver disease recorded in their charts. The main signs of liver disease are shown in table 20.

Table 20. Number and percentage of patients with signs of liver disease

Signs of liver disease	Number of patients	% of patients
Cirrhosis	74	6.2
Varices	44	3.7
Hepatomegaly	32	2.7
Portal hypertension	30	2.5
Ascites	30	2.5
Splenomegaly	28	2.3
Encephalopathy	15	1.3
Liver Tumour/hepatocellular carcinoma	10	0.8
Other	9	0.8

Patients may have more than one sign of liver disease

The vast majority (94%) of these patients had tested hepatitis C PCR positive at some stage. After taking account of PCR status, Males (n=50, 22%) were more likely to have signs of liver disease recorded than females (n=64, 7%). With regard to source of infection, blood transfusion patients and blood clotting disorder patients were more likely to have liver disease signs than anti-D patients. Furthermore, blood clotting disorder patients who were co-infected with hepatitis C and HIV were more likely to have signs of liver disease than those infected with hepatitis C alone. However, the numbers involved were quite small so this finding should be interpreted with caution (table 21).

Table 21. Number and percentage of patients with one or more signs of liver disease by source of infection

Source of infection	Number of patients with signs of liver disease	% of patients
Anti-D	37	4.8
Blood transfusion	56	19.7
Blood clotting disorders	17	15.9
Renal	4	16.0
Total	**114**	**9.6**

Extrahepatic manifestations of hepatitis C infection

According to international literature, approximately 38% of patients with hepatitis C infection will have symptoms of at least one extrahepatic manifestation during the illness. Renal disease, neuropathy, lymphoma, and Sjögren's syndrome with or without cryoglobulinaemia are all strongly associated with hepatitis C infection. Porphyria cutanea tarda and diabetes have also been linked to hepatitis C. Most of the extrahepatic manifestations are immunological, and chronic infection seems to be necessary for their development.[28]

The extrahepatic manifestations that we specifically looked for in the medical charts were Sjögren/Sicca syndrome, diabetes, cryoglobulinaemia, glomerulonephritis, porphyria, neuropathy and lymphomas. However, it was very difficult to determine if these were related to hepatitis C from the medical notes. Conditions that were more likely to be related to the patient's index condition were excluded (e.g. glomeronephritis in renal patients and lymphomas in HIV positive patients). Conditions were also excluded when data in the medical charts indicated that they pre-dated the hepatitis C infection. Diabetes is more likely to be due to obesity than hepatitis C, but our BMI data was too incomplete to assess this.

One hundred patients (8%) had one or more extrahepatic manifestations of hepatitis C infection. Seventy six percent of these had tested hepatitis C PCR positive at some stage. The most common manifestations were diabetes (n=62) and Sjögren/Sicca syndrome (n=20). Dry/gritty/sore eyes were recorded in the charts of 79 additional patients. This was not classified as Sjögren's syndrome unless this term was specifically mentioned in the chart, but it was captured under "other medical conditions". Cryoglobulinaemia syndrome was recorded in the charts of six patients. A further 27 patients had positive tests for cryoglobulinaemia, but this was not recorded as cryoglobulinaemia syndrome (table 22).

Male patients, patients who tested PCR positive at some stage and patients who were older (≥30 years) at infection were more likely to have extrahepatic manifestations of hepatitis C infection.

Table 22. Number and percentage of patients with extrahepatic manifestations of hepatitis C infection

Extrahepatic manifestations	Number of patients	% of patients
Diabetes	62	5.2
Sicca/Sjogren Syndrome	20	1.7
Neuropathy	7	0.6
Cryoglubulinaemia syndrome	6	0.5
Glomerulonephritis	3	0.3
Porphyria	3	0.3
Lymphoma	2	0.2

Other known liver diseases

Sixty one patients (5%) had one or more liver diseases, other than hepatitis C, mentioned in their charts. The most common were alcoholic liver disease (n=11, 1%), liver steatosis (n=9, <1%) and haemochromatosis (n=8, <1%).

Other significant medical conditions

Almost all patients had significant medical conditions, other than hepatitis C or their index condition (e.g. renal disease), described in their charts. These were not necessarily conditions that were diagnosed according to standardised criteria and may be unrelated to hepatitis C infection. Minor or self-limiting conditions (e.g. tonsillectomies and urinary tract infections, unless recurrent) were not included in the database.

Some medical conditions and surgical procedures may be underestimated if they were availed of privately and not discussed with the consultant hepatologist, or if they were not recorded in the medical charts by the patient's doctor.

The most commonly recorded conditions were fatigue or lethargy (30%), depression (27%) and arthralgia or joint pain (24%). Twenty three percent of women had a hysterectomy or other operation on the uterus/pelvic floor. Appendicectomies and cholecystectomies were also quite common (11% of patients). Without a comparison group, it is not possible to determine if the prevalence of these conditions and surgical procedures is different from the general population. The prevalence of many of the most commonly recorded conditions was similar between patients who had ever tested hepatitis C PCR positive and those who had no positive PCR results in their charts (table 23).

Depression was reported in the medical charts of 325 patients. Anxiety was also reported for 24 of these patients and for a further 23 patients. Long-term medications for depression or anxiety were recorded in the charts of 45% of the patients who had depression or anxiety noted in their charts. A further 56 patients were taking psycholeptics or psychoanaleptics, but neither depression nor anxiety were recorded in their charts. Depression was more likely to be reported for females and for patients who tested hepatitis C PCR positive at some stage.

In a survey of this cohort carried in 1998/99, high levels of psychological distress were found, with 35% having anxiety scores of clinical concern and 26% having clinical levels of depression. These levels were similar across the three patient groups of anti-D, transfusion and haemophilia.[1] When followed up for about 17 years after infection, anxiety or depression was reported by 16% of the women infected through anti-D in 1977-79.[2] A study of psychological well-being was carried out in 1997 in a Dublin hospital on a group of 93 women with hepatitis C infection acquired either through anti-D immunoglobulin in 1977 or 1991, or through blood transfusion. Clinical anxiety and depression were diagnosed in 48-50% and 21-25% respectively. These findings were not related to PCR status or liver histology.[29] However, the results of these different studies may not be directly comparable – standardised scoring systems were used in some whereas other results are based on unstructured self-reporting of symptoms to the clinician.

Osteoporosis or osteopaenia were also more likely to be reported for females and for patients with at least one positive PCR result in their charts. Blood transfusion and renal patients were more likely to have hypertension than anti-D or blood clotting disorder patients. This was related to older age and male sex and did not depend on PCR status after taking age and sex into account.

Table 23. Most commonly recorded medical conditions, by PCR status

Medical condition or operation	Number of patients	% of patients	Number ever PCR positive	% ever PCR positive	Number never PCR positive	% never PCR positive
Fatigue and lethargy	356	29.9	231	31.0	125	28.0
Depression	325	27.3	233	31.2	92	20.6
Arthralgia or joint pain	282	23.7	173	23.2	109	24.4
Hysterectomies/other excision of uterus	220	18.5	142	19.0	78	17.5
Hypertension	210	17.6	146	19.6	64	14.3
Osteoporosis/Osteopaenia	132	11.1	97	13.1	35	7.8
Fibromyalgia	131	11.0	91	12.2	40	9.0
Appendicectomy	131	11.0	77	10.3	54	12.1
Cholecystectomy	127	10.7	86	11.5	41	9.2
Osteoarthritis	90	7.6	65	8.7	25	5.6
Dry/Itchy/gritty/sore eyes	85	7.1	60	8.0	25	5.6
Asthma	75	6.3	50	6.7	25	5.6
Helicobacter pylori	73	6.1	50	6.7	23	5.2
Hypothyroidism	69	5.8	47	6.3	22	4.9
Irritable bowel syndrome	63	5.3	39	5.2	24	5.4
Hypercholesterolaemia	60	5.0	24	3.2	36	8.1
Menorrhagia	57	4.8	31	4.2	26	5.8
Hiatus hernia	53	4.4	33	4.4	20	4.5
Anaemia	50	4.2	32	4.3	18	4.0

Liver function tests (LFTs)

The results presented here relate to the most recent LFTs in a patient's chart. Almost all patients had one or more LFT results. This ranged from 84% of patients for alpha-fetoprotein (AFP) to 99% for alkaline phosphatase and bilirubin. The timing of the last LFT is shown in figure 19. The majority of patients had LFTs done in the 1-2 years prior to data collection. Overall, 57% of patients tested had one or more abnormal results on last test, with 80% of those with abnormal results testing hepatitis C PCR positive at some stage (table 24).

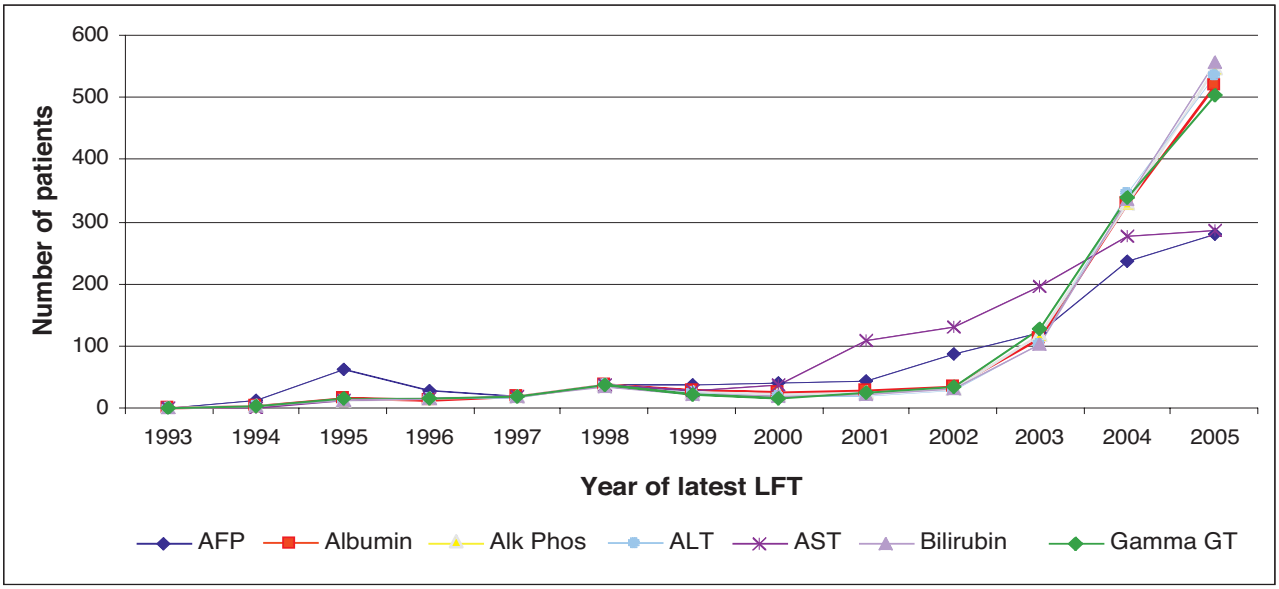


Figure 19. Distribution of year of latest LFT results

Table 24. Number of patients (%) with abnormal LFT results by LFT and PCR status

LFT test	Number patients (%)	Ever PCR positive (%)	Never PCR positive (%)
Elevated AFP	115 (11.4)	97 (14.6)	18 (5.3)
Decreased albumin	108 (9.2)	98 (13.3)	10 (2.3)
Elevated alkaline phosphatase	152 (12.8)	122 (16.4)	30 (6.8)
Elevated ALT	409 (35.2)	375 (51.2)	34 (7.9)
Elevated AST	352 (30.6)	329 (45.6)	23 (5.4)
Elevated bilirubin	101 (8.5)	79 (10.6)	22 (5.0)
Elevated GGT	369 (31.7)	307 (42.1)	62 (14.3)
1 or more abnormal results	**681 (57.3)**	**548 (73.5)**	**133 (30.0)**

Abnormal liver function tests can indicate that something is wrong with the liver. However, the LFT data should be interpreted with caution as patients with quite severe liver damage can have normal LFT results. In addition, abnormally high LFTs are not specific to hepatitis C and also commonly occur as a result of drug or alcohol induced liver damage, muscle injury, biliary cirrhosis and other illnesses.

The actual levels of the LFTs are recorded in the database and are available for further analysis. As we will be recording annual LFT results, it will be possible to track LFT levels over time and relate this to disease progression. For more detailed LFT results see appendix J.

Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)
ALT levels were elevated for 51% of PCR positive and 8% of PCR negative patients tested. Abnormally high ALT results were also significantly more likely in males, patients with cirrhosis and patients infected for longer durations (table 24, appendix J: table 49).

AST levels were elevated for 46% of patients who ever tested PCR positive compared to 5% of those with no positive PCR results. Levels were also more likely to be elevated in patients who were older at infection, had been infected for longer and those with alcohol consumption over the recommended limits (table 24).

ALT and AST are produced in liver cells and are leaked into the circulation when cells are damaged. Abnormally high serum ALT is quite a sensitive indicator of liver damage. AST is less specific for liver damage, with increases also seen after myocardial infarction or skeletal muscle injury.

Gamma glutamyl transpeptidase (GGT)
GGT levels were elevated for 42% of patients who ever tested PCR positive for hepatitis C compared to 14% of those who did not. Elevated GGT levels were also more common in males, patients with cirrhosis and patients who consumed alcohol over the recommended limits (table 24, appendix J: table 50). GGT levels are often normal in patients with chronic hepatitis C, but are generally more likely to be abnormally high in those with cirrhosis.

Albumin
Albumin levels were significantly more likely to be abnormally low for patients who ever tested PCR positive, renal patients, patients who consumed alcohol in excess of recommended limits and patients who were older when infected with hepatitis C. Low levels of albumin indicate impaired protein synthesis by the liver due to liver disease, poor nutritional status or kidney disease. Levels are usually normal in patients with hepatitis C until late-stage disease.

Alpha-fetoprotein (AFP)
Where AFP results were available for patients with HCC/liver tumours (n=9), 78% had elevated levels. Overall, AFP levels were abnormally high for 11% of patients. This differed by PCR status with 15% of patients who ever tested PCR positive for hepatitis C and 5% of patients who had no positive PCR results having elevated AFP. Males, patients with longer durations of infection at test and patients with cirrhosis were also more likely to have elevated AFP levels (table 24, appendix J: table 51).

Serum AFP is the most widely used tumour marker for detecting patients with HCC. When AFP is used for screening of high-risk populations, a sensitivity of 39% to 97%, specificity of 76% to 95% and a positive predictive value of 9% to 32% have been reported (see glossary for explanation of these terms). AFP is not specific for HCC. Titres also rise in acute or chronic hepatitis, in pregnancy, and in the presence of germ cell tumours.[30]

Autoantibody results

Over 90% of patients had at least one autoantibody test and 37% of patients tested had at least one positive result. This varied by source of infection, with blood clotting disorder patients less likely than the other groups to have positive results (table 25).

Table 25. Number and percentage of patients with one or more positive autoantibody results by source of infection

Source of infection	Number of patients who had AUT tests	Number of patients with one or more positive results	% tested who had one or more positive results
Anti-D	732	291	39.8
Blood transfusion	252	97	38.5
Blood clotting disorders	97	11	11.3
Renal	22	9	40.9
Total	**1103**	**408**	**37.0**

Anti-nuclear factor (ANF) and rheumatoid factor (RF) were positive in 22% and 19% of patients tested, respectively. Both were more likely to be positive in females and in PCR positive patients. Matched comparison groups of non-hepatitis C infected people would be needed to interpret of these findings (table 26).

Table 26. Number and percentage of patients with positive autoantibody results by autoantibody test

Autoantibody test*	Number tested	Number positive	% positive	Mean age at positive test	Mean duration of infection at positive test	% of positives female	% of positives ever PCR positive
SMA	1062	100	9.4	47.8	18.3	84.0	70.0
AMA	1062	10	0.9	53.8	18.1	70.0	50.0
ANF	1054	235	22.3	49.9	19.3	91.1	60.4
RF	831	155	18.7	50.2	20.1	89.7	88.4
LKM	676	7	1.0	49.6	16.0	100.0	85.7
DNA	140	14	10.0	50.7	20.9	85.7	71.4

*SMA: Anti-smooth muscle antigen, AMA: Anti-mitochondrial antibody, ANF: Anti-nuclear factor, RF: rheumatoid factor, LKM: liver kidney microsome, DNA: anti-DNA antibodies

HLA (human leucocyte antigen) results

We attempted to collect data on HLA results. However, these were only recorded for 163 (14%) patients and there were too few data to draw any meaningful conclusions. We are aware that some of the units have been carrying out specific and detailed research in this area and if further data were made available through the patient's medical records in the future, this could be reported within the database project.[31,32,33] There may be value in combining and analysing HLA data for the entire cohort and relating them to clinical outcomes.

Liver biopsy results

Seven hundred and forty patients (62%) had one or more liver biopsies. Patients who tested hepatitis C PCR positive at some stage were more likely to have had biopsies (84%) than those who did not (27%). A

total of 1,457 biopsies were done. Some details are missing, most commonly fibrosis scores, for 7% of these. Blood clotting disorder patients were least likely to have biopsies (table 27).

Table 27. Number and % of patients who have had one or more liver biopsies by source of infection and PCR status

Source of infection	Number patients who had liver biopsies (%)	Number ever PCR positive (%)	Number never PCR positive (%)
Anti-D	500 (64.9)	396 (96.8)	104 (28.8)
Blood transfusion	188 (66.2)	177 (78.7)	11 (18.6)
Blood clotting disorders	30 (28.0)	28 (32.9)	2 (9.1)
Renal	20 (80.0)	19 (79.2)	1 (100.0)
Total	**738 (62.2)**	**620 (83.4)**	**118 (26.6)**

2 of the patients who had biopsies had other sources of infection and are not included in this table

Biopsies are usually scored using two systems. The first is the degree of inflammation (grade). This may fluctuate over time and reflects ongoing disease activity and severity. The second is degree of fibrosis (scarring) (stage). This is a better indicator of disease progression. In some individuals, fibrosis can progress to cirrhosis, in which the liver becomes extensively and permanently scarred and no longer functions properly. Cirrhosis is associated with the major complications of liver disease including portal hypertension, liver failure and hepatocellular carcinoma.

Inflammation

Of patients who tested PCR positive at some stage and had a biopsy, 2% had no inflammation on last biopsy, 77% had mild inflammation, 20% had moderate inflammation and 2% had severe inflammation (figure 20).

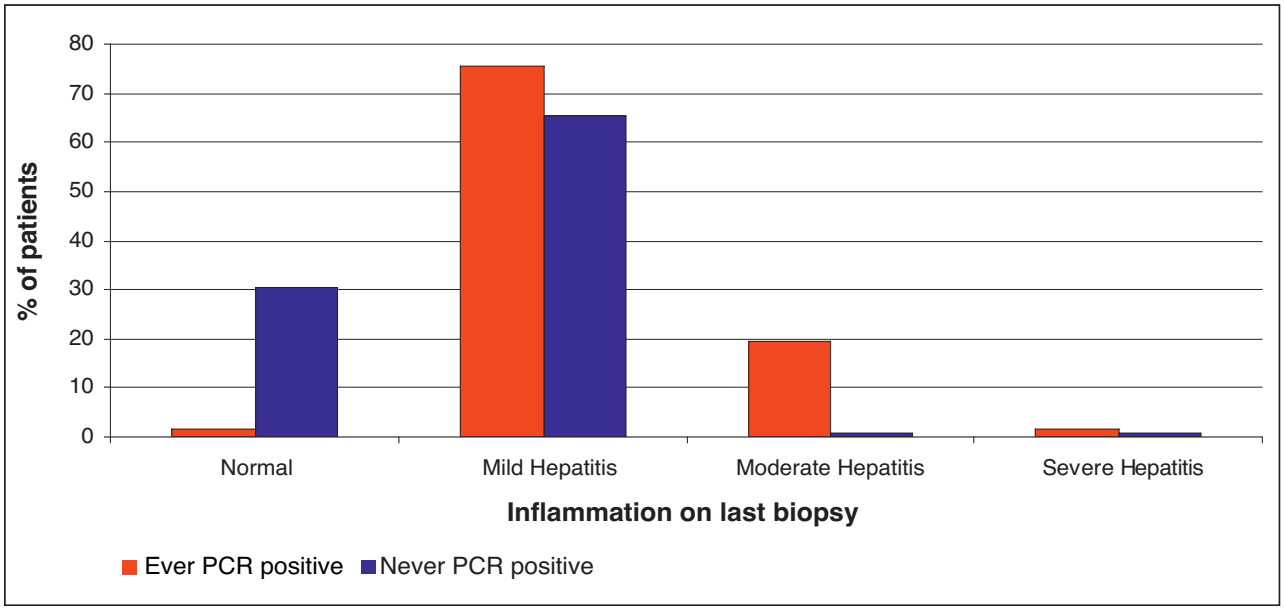


Figure 20. Inflammation on last biopsy by PCR status

Over 90% of biopsies on patients who had no positive PCR results took place within 3 years of their diagnosis and the vast majority of these patients (over 90%) only had one biopsy. Sixty seven percent had mild inflammation on last biopsy. This may reflect background liver inflammation levels, relating to causes other than hepatitis C (obesity, alcohol overuse, diabetes, prescription or non-prescription drugs) (figure 20).

Fifteen percent of anti-D patients, 28% of the blood transfusion patients, 17% of the blood clotting disorder patients and 21% of the renal patients had either moderate or severe inflammation on last biopsy. Blood transfusion patients were more likely to have moderate or severe inflammation on biopsy than the other patient groups (figure 21, appendix J: table 52).

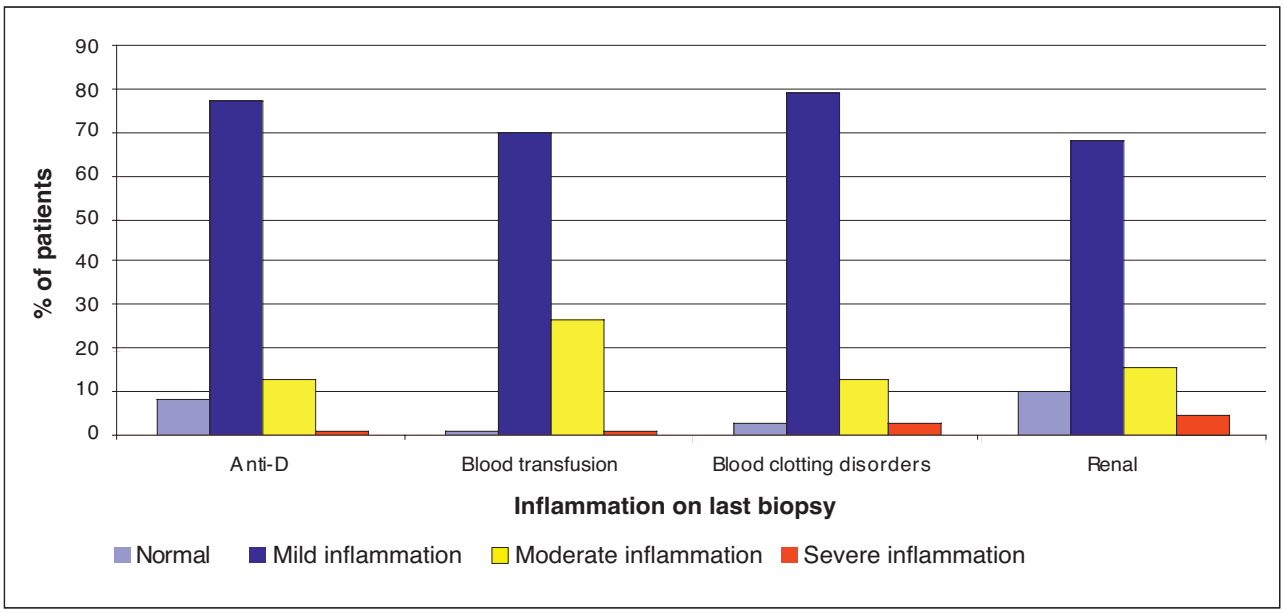


Figure 21. Inflammation on last biopsy by source of infection (both ever PCR positive and never PCR positive patients)

Overall, patients who consumed alcohol in excess of recommended limits, were PCR positive, had been infected for longer durations at last biopsy (25 years or over compared to <25 years) and those who were older at biopsy (50 years or over compared to <50) were significantly more likely to have moderate or severe inflammation (appendix J: table 52).

Fibrosis scores

Fibrosis was scored using different scoring systems in different units. Five hundred and forty three biopsies were scored using the modified Knodell/Ishak/modified HAI system (maximum score is 6, see appendix H for more details). For biopsies scored using this system, 8% of anti-D patients, 30% of blood transfusion patients, 22% of blood clotting disorder patients and 25% of renal patients had scores of 4/5/6. Blood transfusion patients were significantly more likely to have high fibrosis scores (4/5/6). Males, patients who consumed alcohol in excess of healthy recommendations, patients who were older at infection (30+ compared to <30) and patients who had been infected for longer durations (25+ years compared to <25) were also more likely to have high fibrosis scores on their last biopsy (figure 22, appendix J: table 53).

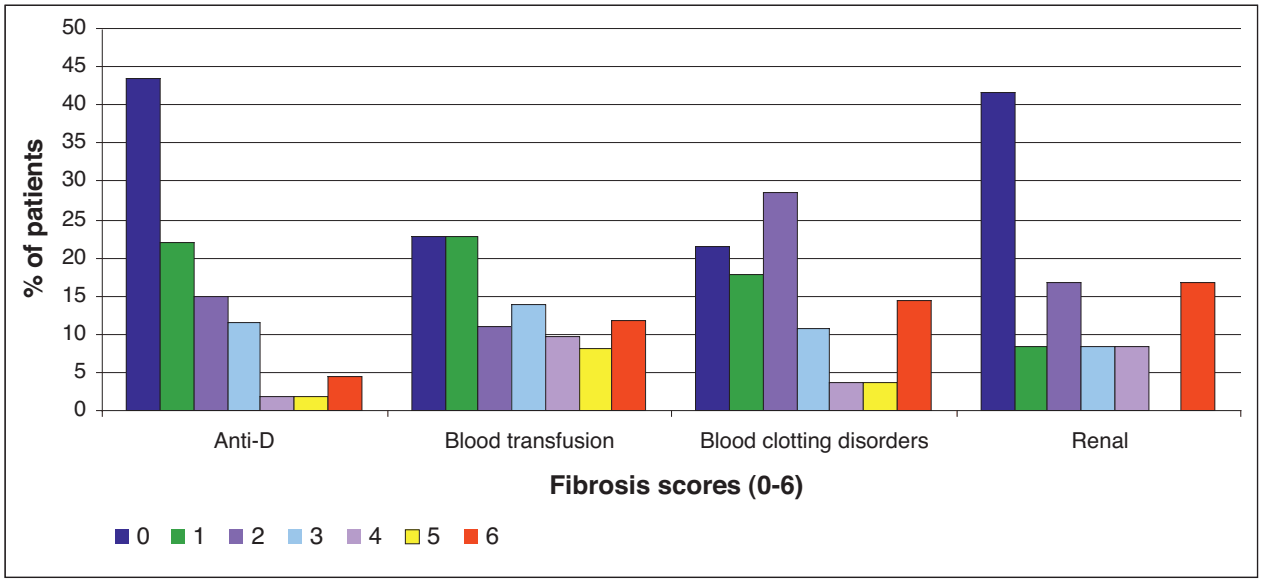


Figure 22. Fibrosis scores on last biopsy by source of infection, for biopsies scored using 0-6 scoring systems (both ever PCR positive and never PCR positive patients)

One hundred and sixty six biopsies were scored using the Knodell, Scheuer or the International Group of Hepatopathologists systems (maximum score is 4, see appendix H for more details). For biopsies scored from 0 to 4, 25% of blood transfusion patients had scores of 3/4 compared to 8% of anti-D patients, but the number of patients with biopsies scored using these systems was low (n=10, for both).

In a large study of patients with chronic hepatitis C, three independent factors were found to be associated with an increased rate of fibrosis progression: age at infection older than 40 years, daily alcohol consumption of 50 g or more, and male sex. The median estimated duration of infection for progression to cirrhosis was 30 years.[9]

In a study of PCR positive women infected through anti-D, pathologists evaluated a representative cross section of liver biopsy samples according to a standardised scoring system, with every fifth sample assessed jointly by two pathologists.[2] It may be helpful to consider taking a similar approach to standardisation of scoring of biopsies on an ongoing basis in the future. The UK HCV National Register has a system of independent scoring and central archiving of liver biopsy specimens.[34]

Cirrhosis

Sixty five patients (9% of those with biopsies and 6% of the total cohort) had cirrhosis on biopsy. A diagnosis of cirrhosis was recorded elsewhere in the medical charts of nine additional patients and is likely to have been identified on biopsy in a previous hepatology unit or in a hospital attended on a private basis. There was variation in the proportion of patients with cirrhosis in the four patient groups, with blood transfusion patients significantly more likely to have cirrhosis on biopsy or mentioned elsewhere in their charts (table 28).

Table 28. Number and percentage of patients with cirrhosis in biopsy results or elsewhere in chart

Source of infection	Number with cirrhosis in biopsy results	Number with cirrhosis in biopsy results or elsewhere in chart	% of patients with cirrhosis	% of ever PCR positive patients with cirrhosis
Anti-D	26	26	3.4	6.1
Blood transfusion	33	39	13.7	16.9
Blood clotting disorders	4	7	6.5	8.2
Renal	2	2	8.0	8.3
Total	**65**	**74**	**6.2**	**9.7**

Ninety seven percent of the patients with cirrhosis were hepatitis C PCR positive. Patients aged over 60 years at last visit to the unit and patients with alcohol consumption over the recommended limits were also more likely to have cirrhosis (appendix J: table 54).

Of the 26 anti-D patients with cirrhosis, 22 can be assigned to the 1977-79 outbreak. Thus 6% of 359 PCR positive patients in this outbreak period have now developed cirrhosis. This figure is higher than that found in two previous studies on this first anti-D cohort carried out over a decade ago. A study in 1994-95 encompassing most of the PCR positive patients from the first anti-D outbreak in 1977-79 found that seven of the 363 (2%) had probable or definite cirrhosis.[2] A study in a Dublin hospital of 87 PCR positive women who received anti-D in 1977 found no cirrhosis or HCC at first liver biopsy in 1994/95 or subsequent biopsy on the 44 who were untreated 5 years later.[35]

A low risk of progression to cirrhosis was found in long-term follow up of a group of women in Germany who were infected with hepatitis C through contaminated anti-D immunoglobulin in 1978-79. At 20 years after infection, stage 3-4 fibrosis (Ishak scoring system[11]) was found in three percent of 220 viraemic patients who had a liver biopsy. None showed incomplete or complete cirrhosis on biopsy although clinical evidence of cirrhosis was found in less than one percent of viraemic patients.[36] At 25 year follow up, stage 3-4 fibrosis was found in nine percent (43 of 490) viraemic patients who had a liver biopsy and 11 (2%) had stage 5 or 6 fibrosis, that is, incomplete or complete cirrhosis. One person had a diagnosis of HCC.[37]

Hepatocellular carcinoma (HCC)
HCC or liver tumours were recorded in the charts of ten patients. This represents 0.8% of all patients and 1.3% of patients who tested PCR positive at some stage. HCC was recorded in the biopsy results of two patients and either a liver tumour or HCC were mentioned elsewhere in the chart of the eight remaining patients. All of these patients tested hepatitis C PCR positive when last tested.

The source of infection was a blood transfusion for six patients, anti-D for two patients and blood clotting disorder for two patients. The median duration between infection and last visit to the unit for patients with HCC or a liver tumour was 26.5 years (range: 8-41). Six of the patients were male and four were female.

Nine have since died. The death certificate was not available for one and death was not related to hepatitis C for another. The underlying cause of death was liver-related for six patients and hepatitis C contributed to death for the remaining patient. The mean age at death was 60.5 years (range: 44-80).

In patients with established cirrhosis the rates of development of HCC range between one and seven per cent per year.[5] Hepatitis C appears to cause HCC as a consequence of cirrhosis rather than having any direct carcinogenic effects. The majority, if not all, of patients with hepatitis C associated HCC have established cirrhosis.[5]

Deceased patients

One hundred and eleven patients, or 9% of the baseline cohort, had died by the end of 2005. Where death certificates were available (n=107), death was directly caused by liver-related disease for 29 patients (27%) (tables 29 and 30). Twenty six (90%) of these were hepatitis C PCR positive. Eighteen (62%) also had indicators of alcohol consumption over the recommended limits recorded in their charts. Hepatitis C was listed on the death certificate as a cause of death for 24 and a contributing condition for 2. The underlying cause of death was coded to chronic viral hepatitis C for 15, liver cell carcinoma for 8, cirrhosis of the liver for 2, hepatic failure for 2, chronic liver disease for 1 and harmful use of alcohol for 1.

Table 29. Number and percentage of patients who have died by cause of death category

Cause of death category	Number of patients	% of patients	% of PCR positive patients
Liver-related disease directly caused death	29	2.4	3.9
Liver-related disease contributed to death*	32	2.7	4.3
Death was not liver-realated	46	3.9	6.2
Death certificates missing	4	0.3	0.5
Total	**111**	**9.3**	**14.9**

*Liver-related to disease was recorded on the death certificate as a contributing condition, but did not directly cause death

Table 30. Number and percentage of patients who have died by source of infection and death category

Source of infection	Number of deceased patients (%)	Number ever PCR positive	Liver-related disease directly caused death	Liver-related disease contributed to death	Death was not liver related
Anti-D	34 (4.4)	22	7	10	16
Blood transfusion	52 (18.3)	45	16	12	22
Blood clotting disorders	13 (12.1)	13	4	5	3
Renal	11 (44.0)	11	1	5	5
Total	**110 (9.3)**	**91**	**28**	**32**	**46**

1 deceased patient had a source of infection other than those listed above

Liver-related disease did not directly cause death, but was recorded as a contributing condition on the

death certificates of 32 additional patients (tables 29 and 30). Hepatitis C was indicated as contributing to death for 30 of these and cirrhosis of the liver and hepatorenal syndrome were recorded as contributing conditions for the remaining two patients. Five of these patients had no positive hepatitis C PCR results in their charts. The most common underlying causes of death for these patients were neoplasms (n=9), HIV (n=4) and renal disease (n=4).

Interpretation of the presence of hepatitis C on the death certificate is difficult, as knowledge of a patient's hepatitis C status may influence the recording of this, regardless of cause of death.[14] On the other hand, there may be a reluctance to record hepatitis C on the death certificate because of concerns about stigmatisation and also about the management of death (including funeral arrangements) as national guidelines on this have not yet been agreed.[38]

Nearly one thousand people who were infected with hepatitis C through blood transfusion have been followed up through the UK HCV National Register. At an average follow up of 11 years after exposure, those infected were at increased risk of dying directly from liver disease compared to the control group, particularly if they consumed excess alcohol, but this difference was not statistically significant.[39] A further follow up of this cohort at 16 years after exposure found that the risk of death directly from liver disease was significantly higher in cases than in controls. There had been 255 deaths among 924 cases (27.6%) and, of these, 34 were considered to have died directly from liver disease. Nearly 30 percent of cases who died directly from liver disease were known to have consumed excess alcohol.[14]

Cumulative survival curves comparing survival from date of infection to date of last visit (or date of death) for patients who ever tested PCR positive and patients with no positive PCR results in their charts are shown in figure 23. Only data for up to 30 years of follow up were considered as too few patients had durations of infection longer than this.

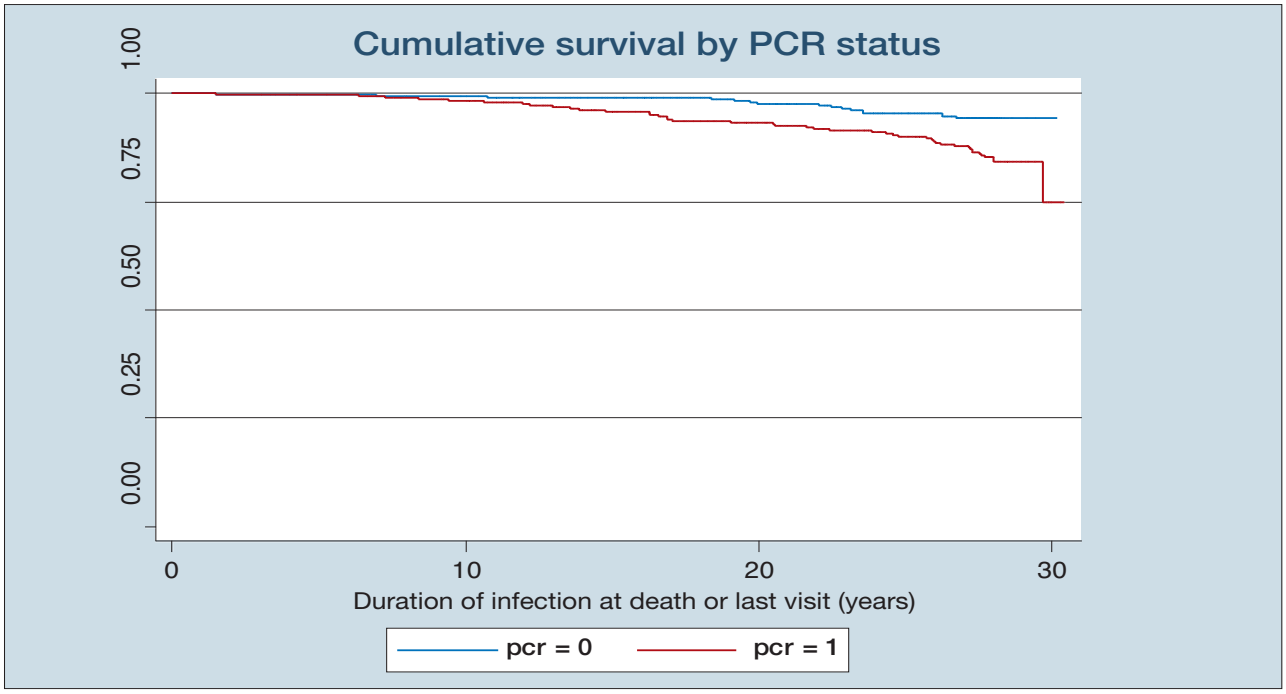


Figure 23. Comparison of survival for patients who ever tested hepatitis C PCR positive and patients who had no positive PCR results in their charts

PCR=0: No positive PCR results in chart, PCR=1, tested PCR positive at some stage

All cause mortality rates were higher for patients who ever tested PCR positive compared to those who never tested PCR positive (Cox regression hazard ratio: 2.62, P<0.001, 95% CI: 1.57-4.38). However, PCR positive patients have only borderline significantly higher all-cause mortality rates once sex, alcohol intake, smoking status and age at infection are taken into account. Mortality rates were higher in patients who consumed alcohol in excess of recommended limits, smokers, males and patients who were older at infection. Blood transfusion, blood clotting disorder and renal patients had higher mortality rates than anti-D patients even after taking account of alcohol intake, smoking status and age at infection (appendix J: table 55).

Looking only at liver-related deaths, patients who ever tested PCR positive had higher mortality rates from liver-related disease (direct causes of death) than patients who never tested PCR positive (Cox regression hazard ratio: 4.26, P=0.010, 95% CI: 1.27-14.31). However, the number of patients for whom liver-related disease directly caused death was low (n=29) and there was no difference between the mortality rates in PCR positive and negative patients after taking account of the effects of alcohol intake and age at infection.

Anti-viral treatment

Background information

Currently the best indicator of effective anti-viral treatment for hepatitis C is a sustained virological response (SVR), defined by the absence of detectable hepatitis C RNA in the serum as shown by a qualitative hepatitis C RNA assay with lower limit of detection of 50 IU/ml or less at 24 weeks after the end of treatment.[7]

Early anti-viral treatment for hepatitis C was with interferon monotherapy (IFN), which had a low SVR, particularly for patients with genotype 1 hepatitis C infections (5-15%, depending on treatment duration). However, response was better for patients with genotypes 2 or 3, with 20-40% achieving SVR.[6]

The current recommended treatment for hepatitis C is combination therapy with pegylated-interferon (peg-IFN) and ribavirin (RBN). Clinical trials with this therapy have found SVRs of between 42 and 46% for genotype 1 patients, and 76 and 82% for genotype 2/3 patients. Lower rates of SVR have been found in trials of IFN and RBN: 33-36% for genotype 1 patients and 61-79% for genotype 2/3 patients.[40,41]

Two hundred and seventy-six patients who ever tested hepatitis C PCR positive (37%) received one or more courses of anti-viral treatment. Five patients with no positive PCR results in their charts were also treated. Some details from the medical charts were missing for three of these, so they may have tested PCR positive at some stage. The remaining two were treated soon after diagnosis in 1994 and 1995. The remainder of this section deals only with the 276 patients who tested PCR positive at some stage.

The distribution of year of first course of anti-viral treatment is shown in figure 24. The percentage of patients treated varied by genotype, age and source of infection. Younger patients (<50 years at last visit) and patients with genotypes 2 and 3 were significantly more likely to be treated than patients with genotype 1. After taking account of genotype and age, blood clotting disorder and blood transfusion patients were more likely to undergo treatment than anti-D patients and renal patients were less likely to be treated (table 31, appendix table 56).

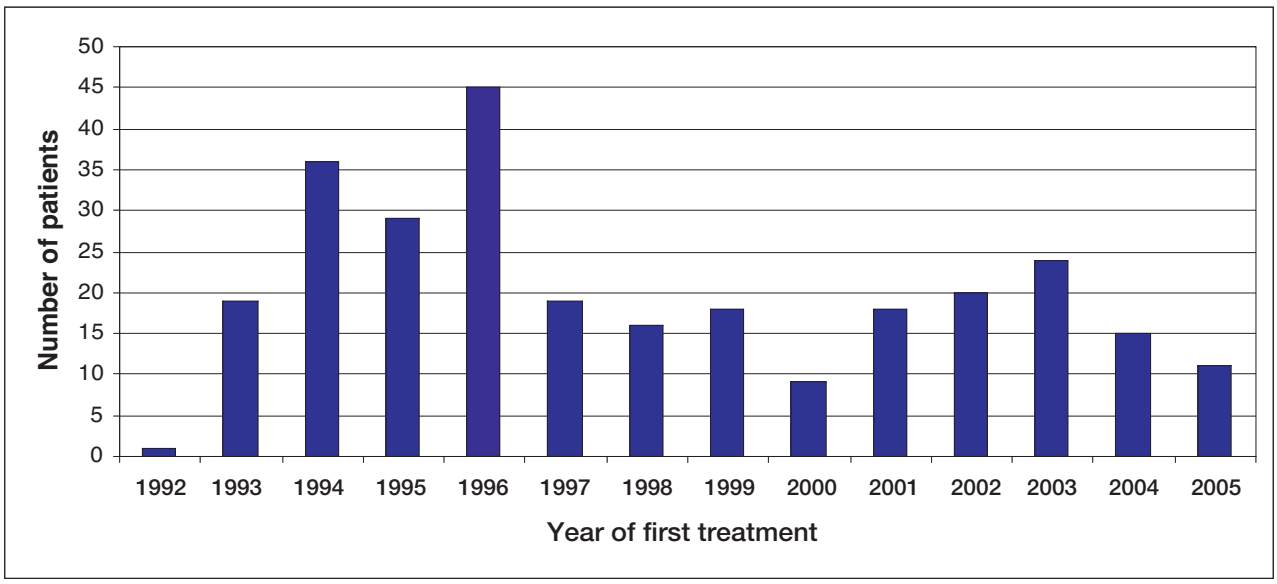


Figure 24. Distribution of year of first course of treatment

Table 31. Number (%) of patients treated by source of infection and genotype

Source of infection	Genotype 1	Genotypes 2 or 3	Total
Anti-D	83 (23.5)	34 (85.0)	117 (29.7)
Blood transfusion	44 (35.2)	64 (70.3)	108 (60.0)
Blood clotting disorders	28 (59.6)	16 (64.0)	44 (61.1)
Renal	0	2 (20.0)	2 (10.0)
Total	**155 (28.9)**	**116 (69.9)**	**271 (38.6)**

1 patient with genotype 5 and 4 patients with no genotypes in their charts were also treated

Treatment outcome: first course of treatment

Treatment response is calculated on an intention to treat basis. Data on patients who were still on treatment at the time of data collection were excluded when calculating response rates, but patients who stopped their treatment early due to side effects were included. Stopping treatment early did not vary by type of treatment, but did vary by source of infection, with blood clotting disorder patients significantly less likely to stop treatment early than anti-D patients (table 32).

Table 32. Number and percentage of patients who stopped first treatment early by source of infection

Source of infection	Number of patients stopping treatment early	% of patients treated
Anti-D	32	29.1
Blood transfusion	25	23.6
Blood clotting disorders	5	11.9
Renal	2	100
Total	**64**	**24.6**

Response to the first course of treatment varied by genotype and treatment regime. For monotherapy with IFN, genotype 1 patients had a SVR of 7% compared to 40% for patients with genotypes 2 or 3. The highest SVR for genotype 1 patients was 29% on peg-IFN and RBN combination therapy. This compares poorly to an SVR of 71% for patients with genotypes 2 or 3 on the same therapy (table 33).

Table 33. Number of genotype 1-3 patients treated and response to first course of treatment by type of therapy received

	Number of patients treated				% Sustained viral response			
Genotype	IFN	IFN & RBN	Peg-IFN & RBN	Total	% SVR IFN	% SVR IFN & RBN	% SVR Peg-IFN & RBN	% SVR all anti-viral therapies
1	75	33	28	137	6.7	27.3	28.6	16.2
2 or 3	62	31	21	114	40.3	58.1	71.4	50.9
All	**137**	**64**	**49**	**251**	**21.9**	**42.2**	**46.9**	**32**

Patients with unknown genotype (n=4) or genotype 5 (n=1) and 1 patient who was on Peg-IFN monotherapy were omitted from this table. 20 additional patients were still on treatment at the time of data collection

Response rates in our cohort were at the low end of ranges found in clinical trials. This is to be expected as adherence to the treatment protocol is likely to be better in clinical trials than in more routine clinical settings.

SVR was improved by increasing the duration of treatment. However, longer treatment durations resulted in less dramatic improvements in SVR for patients with genotypes 2/3 compared to patients with genotype 1. For instance, 67% of genotype 2/3 patients on combination therapy had an SVR after 16-23 weeks, 68% had an SVR after 24-47 weeks and 70% had an SVR after 48 or more weeks of treatment. No genotype 1 patients had an SVR after 16-23 weeks of treatment, 29% responded after 24-47 weeks of treatment and 46% responded after 48 or more weeks of treatment. Tables 34 and 35 and figure 25 show SVR by duration of treatment and genotype for patients on monotherapy and combination therapy.
Overall, being genotype 2/3 rather than genotype 1, being on combination therapy, younger age at treatment (<45 years), longer duration of treatment and shorter duration of infection at treatment (<20 years) significantly improved response rates. Patients with elevated ALT levels on last test were less likely to have an SVR (appendix J: table 57)

Table 34. Number of patients treated with IFN or Peg-IFN monotherapy and percentage SVR by genotype and duration of treatment (first course of treatment)

Monotherapy	Number of patients treated			% SVR		
Genotype	At least 24 weeks	At least 48 weeks	All treatment durations	At least 24 weeks	At least 48 weeks	All treatment durations
1	46	20	76	6.5	10.0	6.6
2 or 3	43	28	62	48.8	57.1	40.3
All	**89**	**48**	**138**	**27.0**	**37.5**	**21.7**

Table 35. Number of patients treated with IFN and ribavirin or Peg-IFN and ribavirin combination therapy and percentage SVR by genotype and duration of treatment (first course of treatment)

Combination therapy	Number of patients treated			% SVR		
Genotype	At least 24 weeks	At least 48 weeks	All treatment durations	At least 24 weeks	At least 48 weeks	All treatment durations
1	43	26	61	39.5	46.2	27.9
2 or 3	35	10	52	68.6	70	63.5
All	**78**	**36**	**113**	**52.6**	**52.8**	**44.2**

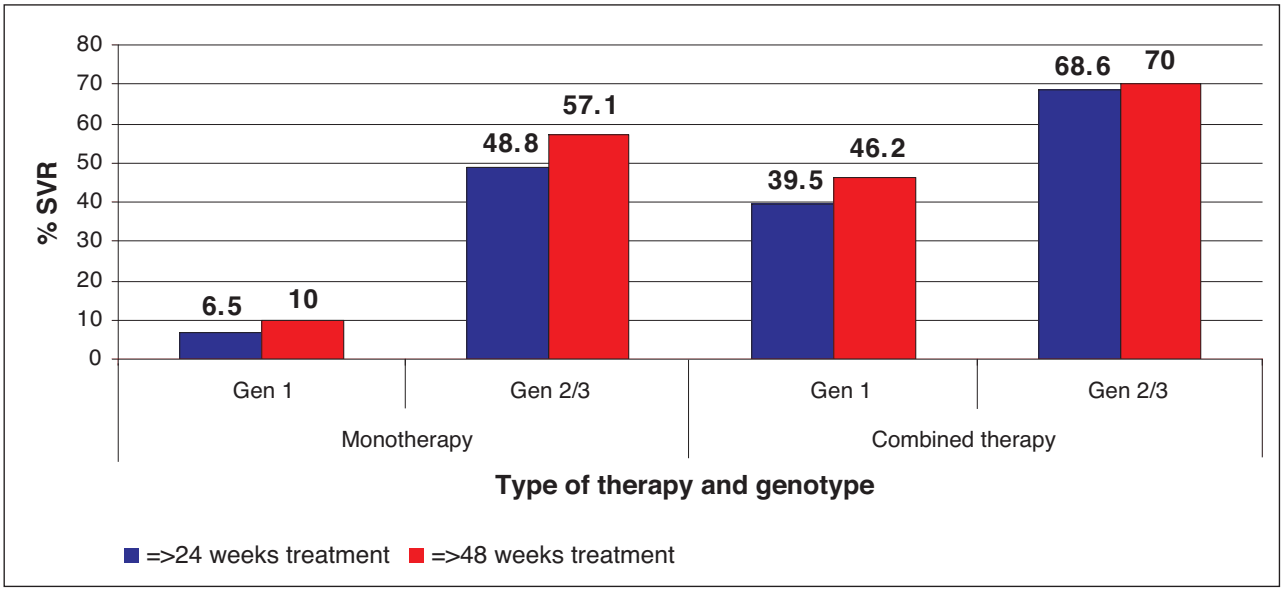


Figure 25. Percentage SVR for treatment naïve patients by genotype and duration of therapy for monotherapy with IFN or Peg-IFN, and combined therapy with IFN and RBN or Peg-IFN and RBN

Treatment outcome: second course of treatment

Seventy three patients underwent a second course of treatment. Eighty five percent of these had previously been on monotherapy with IFN and most of the remainder had been treated with IFN and RBN. On second course, 16 received monotherapy with IFN or peg-IFN, 28 were treated with IFN and RBN and 29 were treated with peg-IFN and RBN. Eight were still on treatment at the time of data collection.

It is difficult to interpret the outcome of treatment for those on monotherapy, as the number of patients was low (table 36). Due to small numbers, patients treated with IFN and RBN are grouped with those treated with peg-IFN and RBN in the tables showing results for the second course of treatment. Twenty three percent of genotype 1 and 56% of genotype 2/3 patients, treated with combination therapy had an SVR on second treatment (table 37). This was only slightly lower than that achieved by patients initially treated with combination therapy (28% for genotype 1 and 63% for genotype 2/3 patients), indicating that re-treatment of patients who had not previously responded achieves good response rates.

Data on treatment will become more important in the future as more patients are treated. More analysis could be done in terms of how patient demographics, hepatitis C genotype, treatment dose, duration and

type affect response. Small numbers have been treated to date. Thirty seven percent is low but is higher than the 18% previously reported for this cohort.[1] The proportion treated is also higher than the figure of 18% reported for the UK transfusion-acquired hepatitis C cohort. However, their figure was for treatment received by May 2002 and may have increased since then. Their cohort was also older at infection and the mean duration of infection was around 10 years.[42]

Table 36. Number of patients treated and response to second course of treatment by genotype and type of therapy received

	Number of patients treated			% SVR		
Genotype	IFN/Peg-IFN	IFN/Peg-IFN & RBN	Total	IFN/Peg-IFN	IFN/Peg-IFN & RBN	Total
1	11	31	42	27.3	22.6	23.8
2 or 3	5	18	23	60.0	55.6	56.5
All	**16**	**49**	**65**	**37.5**	**34.7**	**35.4**

8 patients were still on treatment at the time of data collection

Table 37. Number of patients whose second course of treatment was combination therapy with IFN and Ribavirin or Peg-IFN and Ribavirin and their % SVR after at least 24 weeks treatment

	Number of patients treated		% SVR combined therapy	
Genotype	At least 24 weeks	All treatment durations	At least 24 weeks	All treatment durations
1	22	31	31.8	22.6
2 or 3	14	18	64.3	55.6
All	**36**	**49**	**44.4**	**34.7**

8 patients were still on treatment at the time of data collection

Other long-term medications and complementary and alternative treatments

Long-term medications

The most common long-term medications used were cardiovascular drugs, drugs used to treat depression, anxiety or sleep disorders, drugs for acid-related disorders and anti-inflammatory and anti-rheumatic drugs (table 38).

Table 38. Most common long-term medications recorded

Most common long term medications	Ever PCR pos (%)	No pos PCR results (%)	Total (%)
Drugs for acid related disorders	135 (18.1)	40 (9.0)	175 (14.7)
Psychoanaleptics	112 (15.0)	40 (9.0)	152 (12.8)
Beta blocking agents	76 (10.2)	31 (7.0)	107 (9.0)
Psycholeptics	80 (10.7)	26 (5.8)	106 (8.9)
Diuretics	59 (7.9)	28 (6.3)	87 (7.3)
Antithrombotic agents	54 (7.2)	25 (5.6)	79 (6.6)
Serum lipid reducing agents	27 (3.6)	49 (11.0)	76 (6.4)
Anti-inflammatory and antirheumatic products	45 (6.0)	30 (6.7)	75 (6.3)
Agents acting on the renin-angiotensin system	53 (7.1)	22 (4.9)	75 (6.3)
Thyroid therapy	44 (5.9)	24 (5.4)	68 (5.7)
Mineral supplements	47 (6.3)	19 (4.3)	66 (5.5)
Drugs for treatment of bone diseases	44 (5.9)	17 (3.8)	61 (5.1)
Sex hormones and modulators of the genital system	33 (4.4)	23 (5.2)	56 (4.7)
Analgesics	37 (5.0)	18 (4.0)	55 (4.6)
Drugs for obstructive airway diseases	37 (5.0)	16 (3.6)	53 (4.4)
Drugs used in diabetes	38 (5.1)	15 (3.4)	53 (4.4)
Calcium channel blockers	37 (5.0)	13 (2.9)	50 (4.2)
Corticosteroids for systemic use	35 (4.7)	3 (0.7)	38 (3.2)

Patients may be on more than one type of long term medication

The proportion of ever PCR positive patients taking drugs to treat depression, anxiety or sleep disorders was higher than that for patients with no positive PCR results. This agrees with previous findings of a higher likelihood of depression and anxiety in PCR positive patients (see section on other significant medical conditions). However, it is not possible to interpret the significance of the data on long term medications without comparing them to usage figures for the general population or a suitable comparison group.

Complementary and alternative treatments

Complementary and alternative therapies are increasingly being used in addition to standard therapy and were recorded in the charts of 66 patients (6%). The types of treatment most commonly used are shown in table 39 and include herbal remedies, acupuncture, reflexology and massage. An additional sixty one patients attended a physiotherapist in the twelve months prior to data collection. Some of these may have attended the physiotherapist for massage.

Table 39. Most common complementary and alternative treatments

Complementary and alternative treatments	Number of patients	% of patients
Herbal Remedies	31	2.6
Acupuncture	25	2.1
Reflexology	7	0.6
Massage Therapy	7	0.6
Chinese Medicine	5	0.4
Aromatherapy	5	0.4
Hydrotherapy	4	0.3
Homeopathy	4	0.3

The proportion of patients using complementary and alternative treatments is likely to be underestimated in the database as many patients attend private practitioners for these treatments and these are unlikely to be recorded in their medical charts. The 2000 RCSI survey of a sample of this cohort found that 22% of patients interviewed had tried complementary therapies.[1]

In addition, the Health Service Executive (HSE) expenditure on complementary and alternative therapies has been increasing steadily in recent years. In 2006, total HSE expenditure on private complementary and alternative therapy, for Health (Amendment) Act 1996 (HAA) card holders, was approximately €140,000. This included expenditure on physiotherapy. Other therapies included were massage, hydrotherapy, acupuncture, aromatherapy and reflexology (personal communication, Michele Tait, HSE 2007).

The second review of health services for people with hepatitis C in Ireland carried out by RCSI found that the use of complementary therapies by adults with hepatitis C was reported to have increased significantly in the previous 6-12 months.[38] The complementary therapies in greatest demand were massage, aromatherapy and reflexology. Support organisations reported significant numbers of their membership who would like to avail of complementary therapies, but were unable to due to lack of availability of therapists. A survey of support organisations found that 39% of participants had used complementary therapies in the previous year.[38] A higher proportion of the anti-D group used these therapies compared to other groups and females were more likely to use complementary therapies than males. The most popular therapies were reflexology (66%), massage (58%), aromatherapy (29%) and chiropody (26%). The expectation is that demand for these services will continue to increase steadily. The authors recommended that the role of complementary or alternative therapies in the management of hepatitis C be advocated for as part of a wider framework of evaluation of the use of such therapies in the Irish health system.

Clinical management

Liver transplants

Ten patients have received liver transplants to date. All patients were hepatitis C PCR positive prior to the transplant. The median duration of hepatitis C infection at transplant was 25 years (range: 1-39) and the median age at transplant was 51 years (range: 29-60). One liver transplant patient has since died. Four additional patients have been on a waiting list for liver transplants and three of these have since died.

Hepatology-related care: In-patient and out-patient visits

There were 1,096 live participants in the 12 months prior to data collection. Seventy (6.4%) had in-patient stays during this period and the median number of in-patient stays was one (range:1-4). Liver biopsy was the most common reason for admission (n=45, 64%), with a median length of stay of one day (range: 0-13). The proportion of patients with in-patient stays was considerably lower than the 16% admitted in the 12-month period prior to the RCSI 2000 report.[1]

Seventy four percent of live participants (n=806) attended an outpatient appointment for hepatology-related care in the 12 months prior to data collection. The median number of appointments was two (range:1-30).

Since the information contained in the database comes entirely from participant's hospital-based medical records, it only relates to the use of hospital services and does not contain information on the use of general practitioner services.

Procedures

Three hundred and eleven patients (28% of live participants) underwent procedures in the 12 months prior to data collection. The vast majority of these were diagnostic in nature. X-ray sites included bones, breasts, the urinary system and veins (table 40).

Table 40. Most common procedures undergone in the 12 months prior to data collection

Most common procedures	Number of procedures	Number of patients	% of patients
Upper GI endoscopy	43	42	3.8
Colonoscopy/ileoscopy	22	21	1.9
Liver biopsy	40	38	3.5
Ultrasound	188	167	15.2
CT scan	58	54	4.9
MRI	28	26	2.4
X-ray with barium/contrast	14	14	1.3
Other X-ray	92	71	6.5

Patients may have multiple procedures

Specialist services

Four hundred and forty five patients (41% of live patients) used specialist health services in the 12 months prior to data collection. The most common services attended related to psychiatry, psychology or counselling (table 41).

The national hepatitis C database only contains the information on services attended if these are noted in the patient's medical chart. If services are availed of privately these may not be discussed with the consultant hepatologist and may not be recorded in the chart. They will therefore be under-represented here.

Services commonly attended on a private basis include counselling, physiotherapy, chiropody and complementary therapies. When these services are attended on a private basis, reimbursement is managed through the hepatitis C liaison officers in the HSE for patients eligible under the HAA.

Interpretation of information on specialist service usage would be difficult even if compared with a matched control group, as one of the provisions under the HAA is a preferential appointment system for hepatitis C related referrals to medical specialists, providing for a first appointment within 2 weeks of the referral.[38] Thus, it is likely that the use of specialist services among HAA card holders would differ from the rest of the population by virtue of access.

The information on hospital attendance, service usage and procedures undergone as recorded in the database may be useful for service planning and monitoring trends in service usage. Different approaches can be taken in the collection of this data in the future, depending on what is required by the planners.

Table 41. Most common specialist services attended in the 12 months prior to data collection

Most common services attended	Number of patients	% of live patients
Psychiatry/psychology/counselling	72	6.9
Rheumatology	64	6.1
Haematology	63	6.0
Physiotherapy	61	5.8
Endocrinology	46	4.4
Obstetrics/Gynaecology	46	4.4
Surgical	41	3.9
Dermatology	37	3.5
Cardiology	34	3.3
Dietician/nutritionist	31	3.0
Ophthalmology	31	3.0
Neurology	29	2.8
Orthopaedic	27	2.6
Dental	24	2.3
Urology	22	2.1
ENT	18	1.7
Genito-Urinary Medicine	17	1.6
Plastic surgery	11	1.1
Respiratory	11	1.1
Gastroenterology	10	1.0

Patients may attend multiple services

Hepatitis A and B vaccination status

Hepatitis A and B vaccination status was not recorded in the medical charts for the majority of patients (58% for hepatitis A and 61% for hepatitis B) (tables 42 and 44). Where this information was recorded, 35% of the patients whose most recent hepatitis C PCR result was positive, were vaccinated for hepatitis A and 79% were vaccinated for hepatitis B. It is likely that this is an underestimate of the proportion of patients vaccinated, as vaccines administered by GPs may not be recorded in the patient's chart in the hepatology unit. Reasons for not vaccinating are shown in tables 43 and 45.

Table 42. Hepatitis A vaccination status

Hepatitis A vaccination status	Last PCR test positive (%)	Last PCR test negative or no PCR tests in chart (%)	Total (%)
Vaccinated	82 (13.7)	45 (7.6)	127 (10.7)
Not vaccinated	153 (25.6)	222 (37.3)	375 (31.5)
Unknown status	362 (60.6)	328 (55.1)	690 (57.9)
Total	**597**	**595**	**1192**

Table 43. Reasons for patient not being vaccinated for hepatitis A

Reason for non-vaccination	Number of patients	% of patients
Hepatitis A Immune	191	17.9
Not indicated - PCR negative	129	12.1
Patient declined	16	1.5
Not indicated	6	0.6
Other	4	0.4
Unknown	29	2.7
Unknown vaccination status	690	64.8
Total	**1065**	**100**

Table 44. Hepatitis B vaccination status

Hepatitis B vaccination status	Last PCR test positive (%)	Last PCR test negative or no PCR tests in chart (%)	Total (%)
Vaccinated	166 (27.8)	75 (12.6)	241 (20.2)
Not vaccinated	45 (7.5)	179 (30.1)	224 (18.8)
Unknown status	386 (64.7)	341 (57.3)	727 (61.0)
Total	**597**	**595**	**1192**

Table 45. Reasons for patient not being vaccinated for hepatitis B

Reason for non-vaccination	Number of patients	% of patients
Not indicated - PCR negative	141	14.8
Patient declined	23	2.4
Hepatitis B Immune	14	1.5
Other	15	1.6
Unknown	31	3.3
Unknown vaccination status	727	76.4
Total	**951**	**100**

The National Immunisation Advisory Committee recommends that patients with persistent hepatitis C infection should be vaccinated against both hepatitis A and hepatitis B virus, if not already immune.[43] Patients with chronic hepatitis C infection are at increased risk of fulminant hepatitis and death if they become infected with hepatitis A.[44] In patients with chronic hepatitis C infection, concurrent chronic hepatitis B increases the risk of progressive liver disease.[7]

Appendix J contains additional tables with detailed statistical results.

Chapter 5 Discussion

Hepatitis C infection has emerged over the last two decades as a major cause of illness and death worldwide. However, with the advent of new drug therapies the disease can now be treated successfully in many people. As hepatitis C virus was first identified as recently as 1989, many aspects of the disease in terms of its natural history, factors associated with disease progression and response to treatment remain to be clarified. The National Hepatitis C Database was established to gather important information on an ongoing basis on a group of people with hepatitis C infection acquired through blood or blood products in Ireland. The fact that most of these people have a known date and source of infection and also that they are being regularly followed up through a small number of specialist services allows a unique opportunity to carry out internationally significant research into both the natural history of hepatitis C and its treatment. Collection of information about the use and outcome of investigative and treatment services will also allow for planning of appropriate services for the future.

This report describes the development of the database, the process of recruitment and data collection, and the main findings of the baseline data collected on participants.

The computer application for the database was purpose-built to meet current needs and allow for future modification if required. A high level of security is ensured, and approved by external audit. The database functioned efficiently and effectively throughout the baseline data collection period and no difficulties were encountered. The remote access development described in the next chapter will enhance its usefulness and efficiency.

The starting point for this database was to determine the total number of eligible participants, defined as people known to be infected with hepatitis C through blood and blood products administered within Ireland. This was done by amalgamating and cross-checking lists of patients by all eight hepatology units to ensure there was no duplicate counting. Although there had been estimates of the size of this group, and of sub-groups of it, published previously, this is the first time that an exercise has been carried out to definitively count people. The only members of the cohort not included in the denominator are those who never attended one of the hepatology units, either by choice, because they lived abroad, or had died before the services were set up. These numbers are likely to be low.

The database population includes those who had any hepatitis C antibody positive result, even if this was only a weak EIA or a RIBA indeterminate. The reasons for including non-confirmed cases are explained in the report. However, where it is appropriate, data analysis can be confined to those having a confirmed test.

The baseline participation rate of more than 70 percent in the database is good, given the fact that consent was required and also the sensitive nature of the subject. This response is a tribute to the generous co-operation of the participants, support groups, and staff in the hepatology units. However, we would hope to improve this level of participation considerably over the next few years, particularly in the groups that are under-represented in the database at present: younger people and those with blood clotting disorders. The challenge to us now is to demonstrate the usefulness, quality and security of the database in order to convince non-participants of the value of taking part.

The database contains a large amount of comprehensive and relevant data on over one thousand people infected with hepatitis C. These data will be updated every year so that long-term follow up can be done. Although all participants are considered to be in the cohort of people infected through blood and blood products, they do not form a homogeneous group in many respects such as age at acquisition, sex, co-

morbid conditions and genotype, and much of the data are more appropriately analysed in four groups determined by source of infection.

In general, the quality and completeness of the data in the database is good, with few missing data in important areas of outcome. In addition, double-entry of data from the collection forms to the database will have reduced transcription errors.

One of the main concerns about quality of data was in relation to the year of acquisition of infection, which was not known for some participants. In order to follow the progression of disease forward in time, it is essential to know the starting point. The assumptions we made may have resulted in a bias towards earlier years of infection. Source of infection was also uncertain for a number of people who had more than one exposure. It may be possible to improve the quality of this information in the future by closer linkage between the hepatology units and bodies having definitive data such as the National Virus Reference Laboratory (NVRL), the National Centre for Hereditary Coagulation Disorders (NCHCD) and the Irish Blood Transfusion Service (IBTS). However, within the overall group, there are large cohorts with certain dates and sources of infection and these can be researched more thoroughly.

Another area of concern about missing data is in the recording of alcohol consumption, and the person's height and weight, to allow for calculation of body mass index (BMI). Given the association between both alcohol intake and obesity on the progression of liver disease, it is essential that these be recorded in a systematic way at routine clinic visits. Recording of hepatitis B infection and vaccination status was also poor and should be improved.

Examination of liver biopsies yields important information about disease progression. The database contains the inflammatory grade and fibrosis score for each biopsy performed on each of the participants, if recorded in the hospital chart. This is valuable information that can be followed forward over time. However, the fibrosis scoring system was not standardised throughout all hospitals and thus not all results could be collated for analysis. There is also a subjective element in reporting biopsy results. For these reasons, it may be useful to consider the approach taken by the National HCV Register in the UK where there is centralised archiving and scoring of liver biopsies.

The data collected in the baseline period have allowed us to describe the cohort in terms of demographics, source and duration of infection, hepatitis C infection status, clinical status, signs of disease progression, use of services, and uptake of and response to treatment.

- Over 80 percent of the 1,192 participants are female, reflecting the large group infected through anti-D immunoglobulin. The majority are still attending a hepatology unit on a regular basis. Most participants are now aged between 40 and 65 years. Seventy six percent of the cohort has now been infected for 20 years or more. The literature suggests that disease may progress particularly between 20 and 30 years after infection so follow up over the next decade will be important.

- A total of 63 percent had tested PCR positive at some time. Of the whole cohort, 79 percent had had a confirmatory test positive for hepatitis C. The anti-D recipient group had a significantly lower level of confirmed positive results. Three quarters of all participants, and 90 percent of the anti-D group, were genotype 1. Genotype 1 is associated with a less successful response to anti-viral treatment.

- Ten percent had indicators of excess alcohol consumption. Alcohol intake information was infrequently recorded except at the first visit. Alcohol excess was more prevalent in men. Alcohol is an important factor in the progression of hepatitis C liver disease.

- Ten percent of patients had signs of liver disease recorded in their charts and the vast majority of these were PCR positive. Liver enzyme (ALT and AST) levels were abnormally elevated in about half of all PCR positive patients.

- Twenty one percent of those who were PCR positive and had a liver biopsy had moderate or severe inflammation on the most recent biopsy. Cirrhosis was found in ten percent of PCR positive patients. Ten patients had hepatocellular carcinoma, nine of whom had died.

- One hundred and eleven patients (9.3%) had died. Death was directly due to liver disease in 29 (27%) and 18 of these had evidence of excess alcohol intake.

- On most outcome measures, anti-D patients had more favourable results than the other three patient groups.

- Only 37 percent of PCR positive patients had ever received anti-viral treatment to date. Patients with genotypes 2 or 3 were more likely to be treated. Those in the blood clotting disorder and blood transfusion groups were more likely to have been treated, as were males. Follow up of treatment data and responses over the next few years will be of great interest as more patients are likely to opt for treatment.

- Of the total cohort, 49 percent remain chronically infected. But of those who had a confirmed positive test, 62 percent remain chronically infected and a further 13 percent had cleared the virus following treatment.

There are limitations inherent in this database, given its design. As the information comes only from what is recorded in hospital medical records, it is inevitable that some data are missing or not recorded consistently by different units. We endeavoured to standardise the collection of data by having a trained research nurse do the data extraction according to written guidelines. However, particularly in areas like clinical signs and symptoms, and diagnoses of medical conditions, the data are generally not recorded in a standardised way and will vary considerably from one unit to another. So, although our findings in these areas may be of some interest, special additional studies would be needed to investigate them further. In addition, information on services attended privately will not be recorded in the database. In particular, this is likely to lead to an underestimate of the use of alternative treatments.

Another limitation in the use of the database is the lack of a comparison group of non-hepatitis C infected people. For the main findings we have made comparisons between PCR positive and PCR negative participants. However, non-infected comparison groups, similar to the cases in other respects such as age and sex, are needed in order to interpret many of the findings. This is an area that should now be pursued.

This report demonstrates the type of data contained within the database and the potential for its use by others. There is a considerable amount of information available to be further analysed and interrogated. It will be updated and improved annually. One of the purposes of the database is to facilitate research into hepatitis C. What is presented here is simply a starting point and we hope it will stimulate research questions that may be investigated within the framework of the database project.

There have been many studies carried out to date on samples of this hepatitis C infected population. One of the advantages of this database is that it will allow this group of people to be followed up over many years, rather than through one-off studies. This is particularly important when looking at the natural history of the infection and the response to treatment.

Given the commitment by patients and health professionals alike to the development of this project, we hope that the data will be used to its full potential by legitimate researchers. To this end, a public call for research based on the database will be issued annually and overseen by the Steering Committee.

In summary, the database will allow us to follow this group of people with hepatitis C infection over time in order to better describe the natural history of the infection and to elucidate factors associated with disease progression and successful response to treatment. It will also provide valuable information for planning health services for the future. The success of the project to date is a measure of the interest among people with hepatitis C and health professionals in furthering knowledge about the infection and in helping to plan services for the future. It also indicates the willingness of patients and health professionals to work together in partnership for the good of all.

Chapter 6 Next steps for the database

Dissemination of findings

Feedback to participants and professionals is essential in ensuring ongoing co-operation and commitment to this project. The findings must be brought to the attention of those involved in patient care and planning of services for this patient group. It is also important that significant findings are made available to the international scientific community. This will be done in the following ways:

- This report will be made freely available through the hepatology units, patient support groups, hepatitis C liaison officers and HPSC. It will be available electronically on the HPSC website.
- An annual newsletter summarising the information from the database will be published for participants and other eligible people. It will be made available through the same channels.
- An annual report will be prepared each year presenting the data gathered in the follow-up data collection.
- This report and subsequent reports will be made available to health service managers and others involved in the planning and evaluation of health services.
- A report will be provided to each of the hepatology units annually summarising the data on their patient group.
- Papers will be prepared for submission to peer-reviewed scientific journals.

Use of data for research

One of the objectives of the database is that it should serve as a resource for research into hepatitis C. This objective will be met in the following ways:

- An annual call for research based on the database will be issued and overseen by the Database Steering Committee. Researchers may be interested in further analysing the data or in using the database to facilitate special additional studies.
- Each hepatology unit will be given access to the full dataset relating to their patient group and access to the complete database except for individual and unit identifiers. This will facilitate individual units in carrying out their own research.
- The selection of appropriate comparison groups will now be investigated. These are necessary in order to determine the significance of many of the findings in hepatitis C infected people.

Improvements to the database

We will continue to work to improve the database in terms of both participation rate and quality of the data.

The aim is to improve the participation rate to at least 90 percent. Very few of those who are not currently participating have actually refused to consent, rather they have not responded to the invitation. We hope that by demonstrating the work already done we may engender confidence and show the usefulness of the database, and thus encourage non-responders to consider participating now. For people who would like to

participate and have not yet consented, consent forms are available through the hepatology units. As patients attend hepatology units for routine visits they will be reminded about the database by the clinical staff. Already this has resulted in new participants joining since the baseline collection period. In addition, the four patient support groups are committed to the project and continue to encourage their members to join up as opportunities arise.

In the coming year, we will investigate if it is possible to reach those eligible patients who have never attended one of the hepatology units and who therefore have not yet been invited to participate.

There are a few areas of data quality that we hope to improve in the coming year. The standardisation of liver biopsy scoring and the possibility of central archiving and scoring of biopsy samples will be considered by the Database Scientific and Technical Group. A consultant histopathologist will be invited to join the Scientific and Technical Group. The Group will also explore ways in which to improve the recording of data on patients' weight, height, alcohol intake and hepatitis B markers and vaccination status.

It may be possible to improve the quality of information on date and source of infection by closer linkage between the hepatology units and bodies having definitive data such as the NVRL, the NCHCD and the IBTS.

Follow-up data collection and maintenance of the database

The first year of annual follow-up will be 2007. This data collection is already well underway by a database research nurse. An annual report will be produced in 2008.

As well as the planned annual data collection process, the database needs to be maintained and updated as new participants are recruited. These may be people who previously chose not to respond, or those who are newly diagnosed or have attended a hepatology unit for the first time. It is essential that we continue to have the services of an experienced research nurse to do the data collection nationally, to ensure high quality information and efficient data collection.

Recent database development

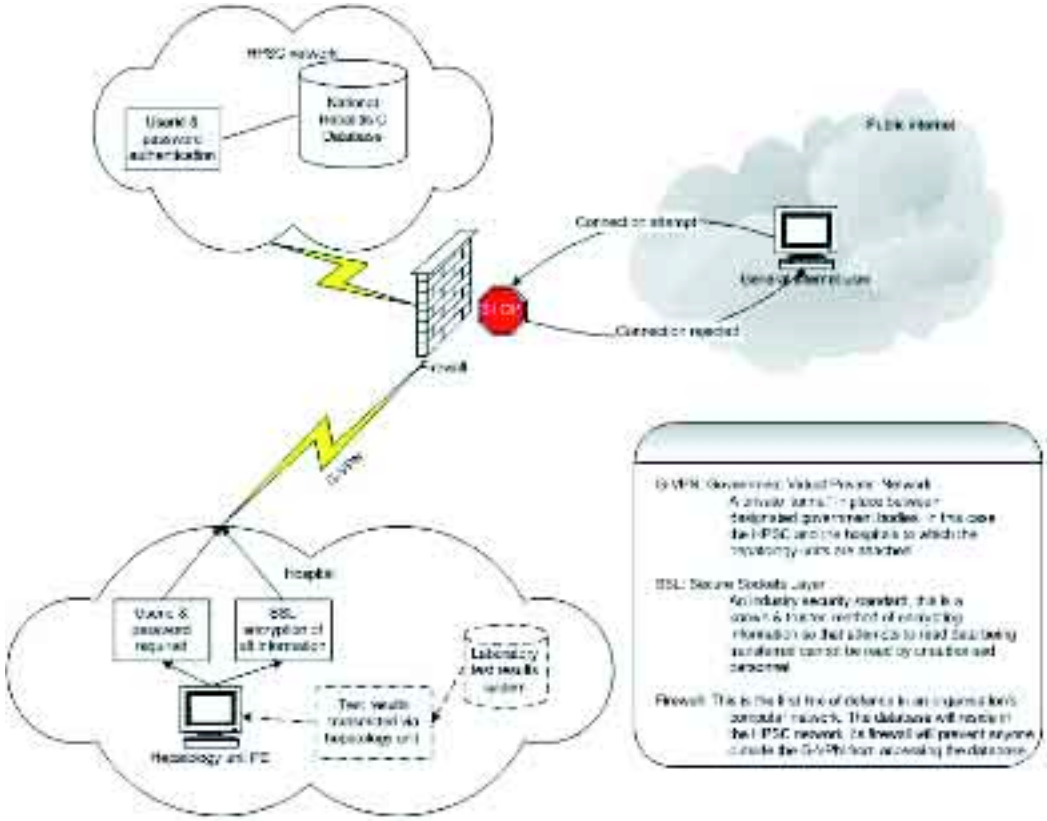
In 2007, the database was upgraded to a web-technology based system allowing the entry of data by a database research nurse to be completed on-site in the units and so reduce the need for paper forms. The database now resides in an MS SQL Server 2005 framework and is accessed via a web client, built using ASP technology. Business Objects is still used to access the database for reporting and analysis.

Permissions to access and edit the database continue to be allocated on a 'least privilege required' principle. Access to the database is restricted to the G-VPN (Government Virtual Private Network). This is a virtual private network for state bodies and is not available on the public internet. SSL (Secure Sockets Layer) technology is employed to encrypt information transferred to and from the database. Each user accessing the database must supply a valid user id and password, which is authenticated using MS SQL Server security.

HPSC is an ISO 27001 certified organisation. ISO 27001 is an international standard of excellence relating to the handling and security of information. HPSC is audited regularly by auditors accredited by the NSAI (National Standards Authority of Ireland) in order to retain this certification and the hepatitis C database (remote access version) is now included in this audit process.

It is proposed that an automated interface to each hospital laboratory system be developed in the future to allow the electronic collection of information, as a second phase of this remote access solution.

Remote access solution



The advantages of this development are as follows:

- **Access to data.** This system allows staff at the hepatology units to view data entered for their patients.
- **Streamlined data collection process**. Using this system, the database research nurse enters data directly in the database. Previously, information was hand-written in forms, transported back to HPSC and entered into the database.
- **Immediate capture of data.** Once data are entered on the system, the information is captured immediately and included in back-up routines.

Advantages of an automated interface from the hospital laboratory systems:

- **Time saving.** Hand-writing of test results into a data collection form will no longer be needed. There will be reduced data entry, and double-entry of test results will no longer be required.
- **Quality of data.** There will be no risk of transcription errors.
- **Foundation for receiving other information.** Once the system is proven to work effectively, the interfaces could be modified to include biopsy results, surgical procedures and other information in the future.

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Appendix A

Members of the National Hepatitis C Database Steering Committee

Dr Declan Bedford, Health Service Executive, North East

Ms Emer Bolger, Beaumont Hospital

Dr Barbara Coughlan, UCD School of Nursing

Ms Margaret Dunne, Irish Haemophilia Society

Ms Susan Gaughran, Transfusion Positive

Professor John Hegarty, St Vincent's University Hospital (Alternate: Dr Suzanne Norris, St James's Hospital)

Ms Lara Hynes, Department of Health and Children (Chair)

Ms Maura Long, Transfusion Positive

Mr Mark Murphy, Irish Kidney Association

Ms Niamh Murphy, Health Protection Surveillance Centre

Ms Eleanor O'Mahony, Positive Action

Ms Michele Tait, Hepatitis C Liaison Officer, Health Service Executive

Dr Lelia Thornton, Health Protection Surveillance Centre

Ms Noeleen White, Positive Action

Former members of the committee

Ms Aline Brennan, Health Protection Surveillance Centre

Ms Maria Fleming, Hepatitis C Liaison Officer, Health Service Executive

Ms Paula Kealy, Positive Action

Ms Ann McGrane, Department of Health and Children

Appendix B

Members of National Hepatitis C Database Scientific and Technical Group

Dr Billy Bourke, Our Lady's Children's Hospital, Crumlin

Dr Garry Courtney, St Luke's Hospital, Kilkenny

Dr Orla Crosbie, Cork University Hospital

Prof John Crowe, Mater Misericordiae University Hospital

Prof John Hegarty, St Vincent's University Hospital

Dr John Lee, University College Hospital, Galway

Ms Carol McNulty, St Vincent's University Hospital

Ms Niamh Murphy, Health Protection Surveillance Centre

Dr Frank Murray, Beaumont Hospital

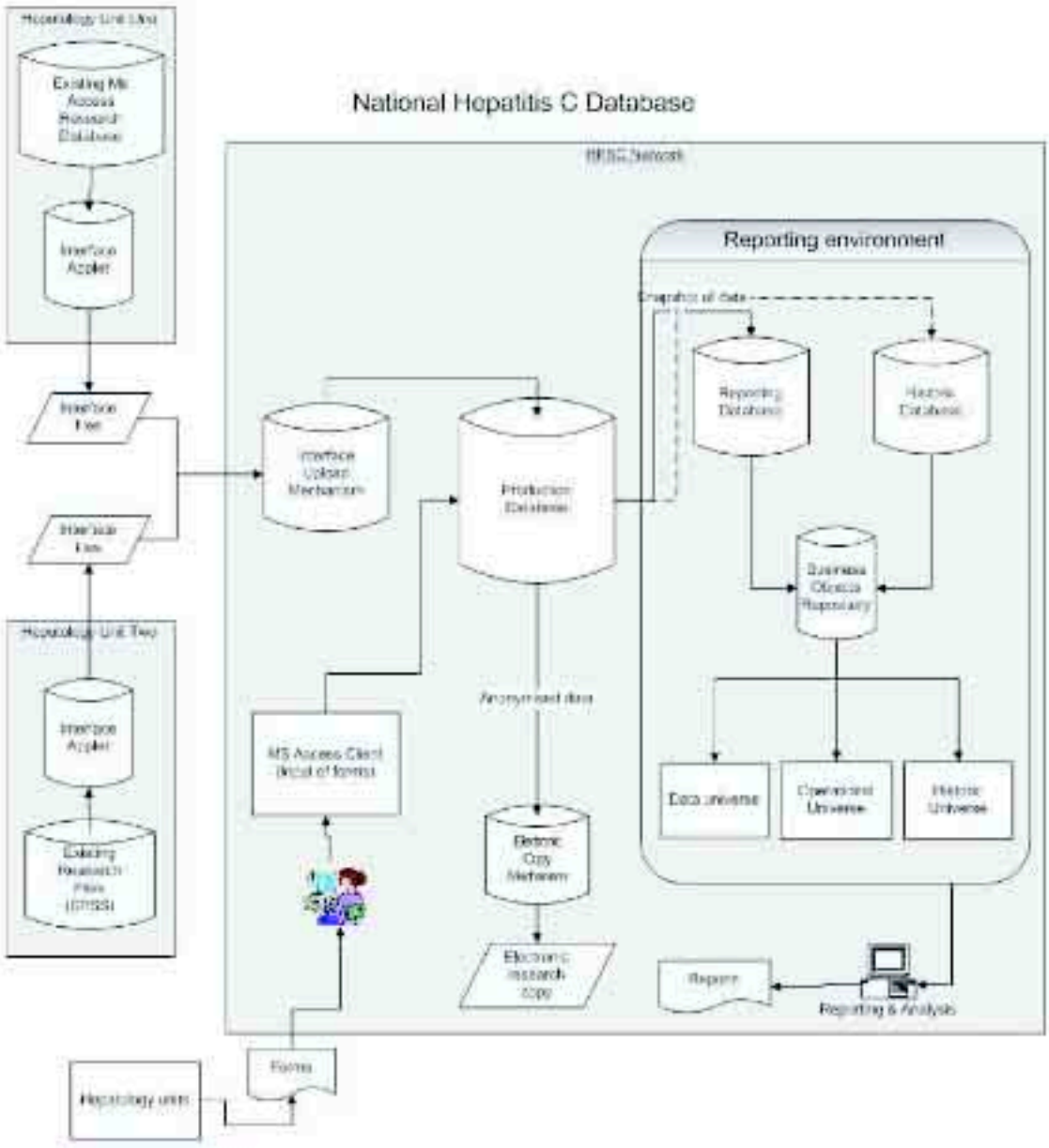
Dr Suzanne Norris, St James's Hospital

Prof Cliona O'Farrelly, St Vincent's University Hospital

Dr Lelia Thornton, Health Protection Surveillance Centre

Appendix C

Database diagram



National Hepatitis C Database
Production Database:
Reporting Database:
Historic Database: This is a snapshot of the production database at a particular point in time. Read only. Allows historic reporting.
Repository: A key Business Objects construct to manage access to the universes, and the translation of user requests into valid database queries.
Data Universe: This presents patient related data - to be used for research & analysis purposes.
Operational Universe: This presents form related data (ie all forms in the database) - to be used for operational queries.
Historic Universe:

Appendix D: Letter sent to eligible patients

Hepatologist name
Hospital name &
address
Date

Dear

I am writing to you to tell you about a new database (a type of register) that is being set up. The Consultative Council on Hepatitis C recommended that a national database of people infected with hepatitis C through blood and blood products be set up so that research could be carried out into this disease. The National Disease Surveillance Centre is now setting up this database in conjunction with the designated hepatology units around the country.

Enclosed with this letter are a leaflet containing more information about this database and a consent form. Please read the leaflet carefully.

You will only be included on the database if we receive a signed consent form from you agreeing to participate.

If you agree to participate we will pass certain information from your medical notes to the database on a regular basis (around once a year). You will not need to provide any of this information yourself. No names or addresses will be held in the database. It will not be possible for you to be identified from reports produced from the database.

If you wish to participate please fill in and sign the consent form and return it to me using the prepaid envelope provided. This consent form will be kept in the hepatology unit, you may get a copy of it at any time.

The aims of the database are to learn more about the range of disease caused by hepatitis C, and also to provide information for the planning of services needed by people infected with hepatitis C in the future. To get an accurate picture of the disease caused by Hepatitis C it is important that as many people as possible participate. Reports and newsletters containing results from the database will be produced on a regular basis. These will be available through the patient support groups and hepatology units.

If you do not wish to participate at the moment you can join up later, and you are also completely free to withdraw at any time. Your medical care will not be affected in any way if you choose not to participate, or if you withdraw at a later time.

If you want any further information you can contact me, or any of the other organisations whose details are given on the enclosed leaflet.

Yours sincerely,

Signed _____

(Consultant Hepatologist)

Appendix E: Patient information leaflet

Who will have access to the database?

Access to the database will be strictly controlled. Apart from relevant staff within the NDSC and the hepatologists from the designated hepatology units having access, other requests for information will have to be approved by the Database Steering Committee.

How can I help?

If you would like to participate in this database please read and sign the consent form and return it to your consultant at the hepatology unit you are attending (or if you are no longer attending one of the eight listed units, the unit you last attended). To get a complete picture of hepatitis C infection in people infected through blood and blood products it is really important that as many people as possible participate in the database.

What if I do not want to participate?

If you do not wish to participate, please return the consent form to your consultant hepatologist indicating you do not wish to participate. If you choose not to participate your care will not be affected in any way.

I'm still not sure, where can I get more information?

You can get more information from your own consultant hepatologist, or from any of the organisations listed on the back of this leaflet.

Irish Haemophilia Society
Iceland House
Arran Court
Arran Quay
Dublin 7.
Email: *haemophiliasociety@eircom.net*
Phone: (01) 8724466
Fax: (01) 8724494
Website: *www.haemophilia-society.ie*

Irish Kidney Association
Donor House
Block 43A
Parkwest
Dublin 12.
Email: *info@ika.ie*
Phone: (01) 668 9788 / 668 9789
Fax: (01) 668 3820
Website: *www.ika.ie*

National Disease Surveillance Centre
Aline Brennan/Dr Lelia Thornton
25-27 Middle Gardiner Street
Dublin 1
Email: *hcvdatabase@ndsc.ie*
Phone: (01) 8765300
Fax: (01) 8561299
Website: *www.hcvdatabase.ie* or *www.ndsc.ie*

Positive Action
56 Fitzwilliam Square
Dublin 2
Email: *posact@indigo.ie*
Phone: (01) 676 2853
(9.30am - 5.00pm Mon - Fri)
Fax: (01) 662 0009

Transfusion Positive
3 Clanwilliam Square
Dublin 2.
Email: *transfusionpositive@eircom.net*
Phone: (01) 6398855 / 6398857
Fax: (01) 6398856

Jul/04

National Hepatitis C Database

for infection acquired through blood and blood products

Patient Information Leaflet

What is the National Hepatitis C Database for infection acquired through blood and blood products?

A clearly defined group of people in Ireland were infected with the hepatitis C virus by contaminated blood or blood products. This presents an important opportunity to study the disease caused by hepatitis C. The Consultative Council on Hepatitis C recommended that a national database, located at an independent coordinating agency, should be set up for research purposes. The database (a type of register) is a way of collecting medical information on the people who were infected with hepatitis C in this way.

Why do we need this database?

The virus that causes hepatitis C was identified relatively recently. Doctors are still learning about the kind of illness it can cause. By collecting medical information on people who were infected with hepatitis C the Hepatitis C Database will help us to learn more about the disease caused by the hepatitis C virus.

It can also be used to help in planning the services needed in the future by those who have hepatitis C infection.

Who can participate?

Anybody who has been infected with hepatitis C through the administration of blood and blood products within the state is eligible to participate. People who have ever attended one of the eight designated hepatology units (St Vincent's University Hospital, St James's Hospital, Beaumont Hospital, the Mater Misericordiae University Hospital and Our Lady's Hospital for Sick Children, Crumlin, in Dublin and St Luke's General Hospital in Kilkenny, Cork University Hospital and University College Hospital Galway) will be invited to participate. Others not identified in this way may also join at any time.

What kind of information will the database contain?

If you agree to participate, we will ask your consultant to pass on information from your medical notes to the database. We will be asking for the following kinds of information:

- Age
- Sex
- How you became infected
- Your medical condition
- Results of tests
- Treatments received

The database will NOT contain people's names or addresses. We will collect your initials and date of birth so that we can identify duplicates (i.e. people who have attended more than one hepatology unit).

Where will the database be located?

The database will be located in the National Disease Surveillance Centre (NDSC). The National Disease Surveillance Centre is Ireland's leading specialist centre for surveillance of communicable diseases. The centre was set up in 1998 conjointly by Ireland's eight Health Boards and with the approval of the Minister for Health and Children.

Who will oversee the database

The Database Steering Committee will oversee the running of the database. Its membership includes representatives from the patient support groups, the consultant hepatologists and the Department of Health and Children.

Appendix F: Patient consent form (back copy)

PATIENT CONSENT FORM
(Adult)

National Hepatitis C Database
for infection acquired through blood and blood products

Please complete this form and return it to the consultant hepatologist in the envelope provided

---

The National Hepatitis C Database for infection acquired through blood and blood products has been set up to collect information on the medical condition of people infected with hepatitis C through contaminated blood or blood products. The database will allow research into the disease caused by hepatitis C and will facilitate service planning for the future needs of infected people.

Participation in the database will mean that selected data in your medical records will be passed on to the National Disease Surveillance Centre on a regular basis. **No names or addresses will be held in the database**, only initials and date of birth will be recorded in the database.

This consent form will be held in the hepatology unit. You can get a copy of it from your hepatology unit at any time. The National Disease Surveillance Centre will keep the bottom copy of this form (**without your name or signature**).

I have read and understood the patient information leaflet about the National Hepatitis C Database. I understand that participation is voluntary and I can withdraw at any time. I understand that if I choose not to participate my health care will not be affected in any way.

Please tick one of the following:

☐ I agree to participate

☐ I do not agree to participate

Date _____

FOR OFFICIAL USE ONLY (to be completed by hepatology unit)

Database no. ☐

Initials ☐

DOB ☐

DD/MM/YY

Appendix G: Baseline data collection form

National Hepatitis C Database

for infection acquired through blood and blood products

Patient Registration Form

1. Database ID _____ 2. Date consent given (dd/mm/yy): | | |

3. Form completed by 4. Date form completed (dd/mm/yy): | | |

5. Hepatology Unit currently (or most recently) attended

- ☐ Beaumont Hospital, Dublin (BH)
- ☐ Cork University Hospital (CUH)
- ☐ St James's Hospital, Dublin (SJH)
- ☐ St Luke's General Hospital, Kilkenny (SLGH)
- ☐ St Vincent's University Hospital, Dublin (SVUH)
- ☐ The Mater Misericordiae University Hospital, Dublin (MMUH)
- ☐ University College Hospits , Galway (UCHG)
- ☐ Our Lady's Hospital for Sick Children, Crumlin, Dublin (OLHSC)

6. Hepatology Unit(s) attended previously: _____

Section 1. Patient Details

7. Patient initials _____ **8. Date of birth** (*dd/mm/yy*) ___/___/___ **9. Sex** Male ☐ Female ☐

10. Height _____ (units) **11. Weight** (*most recent recorded*) _____ (units _____)

12. Ethnic group: White ☐ Black ☐ Asian ☐ Other, specify

13. Country of birth: Ireland ☐ Other, specify _____ **14. Current county of residence**

15. Occupation (*as recorded in medical record*)

16. Birth history (*if female*) Total number of pregnancies Number of live births

17. Alcohol intake (*units/week*)

	Non-Drinker	1-14	15-21	22-49	>49
At first visit to hepatology unit	☐	☐	☐	☐	☐
At last visit	☐	☐	☐	☐	☐

18. Smoking status (*cigarettes/day*)

	Non-Smoker	1-20	>20
At first visit to hepatology unit	☐	☐	☐
At last visit	☐	☐	☐

19. Year of hepatitis C diagnosis _____

20. Most likely source and year of infection (*please tick ONE*)

	Source	Date or Year
☐	Anti-D	_____
☐	Blood transfusion	
☐	Treatment for Haemophilia	_____
☐	Treatment for renal disease	
☐	Other, specify	_____

21. If anti-D:

Anti-D batch number

Hospital at which anti-D was administered _____

22. Other possible blood/blood product exposures (*please give details, including year(s) of exposure(s)*)

_____

_____

_____

_____

_____

23. Other known risk factors Yes ☐ No ☐

If yes, specify

24. Other significant viral infections

HIV positive: Yes ☐ No ☐ Not tested/Unknown ☐

Hepatitis B test results:

	Pos	Neg	Not tested/Unknown
HBsAg	☐	☐	☐
HBcAg			
Anti-HBs	☐	☐	☐
Anti-HBc	☐	☐	☐
Anti-HBe	☐	☐	☐

Other significant viral infection(s)

_____

25. Other known liver disease (*please list*)

_____

26. Other significant medical conditions (*please list*)

_____

_____

27. Patient death recorded Yes ☐ No ☐

If yes, date of death (*dd/mm/yy*): ___/___/___

cause of death

Section 2. Clinical Status

28. Signs of HCV related liver disease ever recorded?

Yes ☐ No ☐ *If yes, please specify below*

	At 1st visit	Anytime since 1st visit
Ascites	☐	☐
Varices	☐	☐
Bleeding varices	☐	☐
Liver tumour/HCC	☐	☐
Encephalopathy	☐	☐
Other (please specify)	☐	☐

29. Extrahepatic manifestations of HCV infection

Yes ☐ No ☐ *If yes, please specify below*

- ☐ Cryoglobulinaemia
- ☐ Glomerulonephritis
- ☐ Porphyria
- ☐ Cutaneous vasculitis
- ☐ Neuropathy
- ☐ Lymphoma
- ☐ Sicca / Sjögren syndrome
- ☐ Diabetes
- ☐ Other (please specify)

Section 3. Clinical Management

30. Date of first visit *(dd/mm/yy)* | |

31. Date of most recent visit for HCV related care *(dd/mm/yy)* | | | If > 12 months ago, skip to question 34

32. Hepatology related care *(in the last 12 months)*

☐ Outpatient
Number of appointments attended

☐ Inpatient (including day care). Please give details of each episode:

Main reason for admission	Length of stay (nights)*

* for day cases please record the number of nights as 0

33. Procedures undergone *(in the last 12 months)*

	No. of times
☐ Diagnostic gastroscopy	
☐ Therapeutic banding gastroscopy	
☐ Therapeutic injection gastroscopy	
☐ TIPPS	
☐ Ultrasound	
☐ CT	
☐ MRI	
☐ Hepatic angiography	
☐ Other *(specify procedure and no. of times)*	

34. Other medical/surgical/psychiatric services attended/referred to *(in the last 12 months)*

35. Other specialist healthcare services (including physiotherapy and dental) attended/referred to *(in the last 12 months)*

36. Fully vaccinated for:

	Yes	No	Unknown	If no, reason:
Hepatitis A	☐	☐	☐	
Hepatitis B	☐	☐	☐	

37. Liver transplant recipient Yes ☐ No ☐

If yes, date *(dd/mm/yy)*: |

	Yes	No
If no, ever on waiting list?	☐	☐
Currently on waiting list?	☐	☐

Section 4. Test Results

38. HCV antibody tests

	Date of test *(dd/mm/yy)*	Pos.	Neg.	Weak
EIA (earliest recorded)		☐	☐	☐

RIBA *(please record banding pattern of first and last OR if banding not available, record results as pos/neg/ind)*

	Date of test *(dd/mm/yy)*	C100	C33	C22	NS5		Pos.	Neg.	Ind.
First						OR	☐	☐	☐
Last									

39. Liver function tests (LFTs) *(most recently carried out in this unit)*

Date *(dd/mm/yy)* | |

Results:

	ALT	INR	PTR
	AST	AFP	
	Bilirubin	Alk Phos	
	Albumin	Gamma GT	

40. Autoantibodies *(most recent)* Date *(dd/mm/yy)* | |

	Pos.	Neg.	Titre		Pos.	Neg.	Titre
ANF	☐	☐		RF	☐	☐	
AMA	☐	☐		DNA	☐	☐	
SMA	☐	☐		LKM	☐	☐	

41. HCV PCR *(record ALL; continue in section 6 if necessary)*

Date of test *(dd/mm/yy)*	Pos.	Neg.	Viral load *(copies/ml)*
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	

42. HCV genotype:

Subtype ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

Sequence information ☐ 1977 ☐ 1991

43. HLA type *(allele 1/allele 2)*

Class I		Class II	
A	/	DR	/
B	/	DQ	/
C	/	DP	/

44. Liver biopsy Yes ☐ No ☐ If yes, give details of ALL below:

Laboratory reference no.	Date of biopsy (dd/mm/yy)	Chronic hepatitis: None	Mild	Moderate	Severe	Fibrosis score	Scoring system	Cirrhosis	HCC

Section 5. Treatment

45. Received anti-viral treatment for HCV Yes ☐ No ☐ If yes, please give details of ALL courses below

Date		Medication 1			Medication 2			Response (see codes below)
Started	Finished	Name/preparation	Dose	Schedule	Name/preparation	Dose	Schedule	

Codes for response to treatment

1: Not relevant (still on treatment)
2: Treatment stopped early (e.g. due to side effects)
3: No response (never became PCR negative)
4: Breakthrough relapse (initial response but became PCR positive while still on treatment)
5: Early relapse (became PCR positive <3/12 after treatment completed)
6: Late relapse (PCR negative >3/12 after treatment but became positive at a later date)
7: Sustained response (remains PCR negative >3/12 after treatment completed)
8: Long term response (remains PCR negative 12/12 after treatment completed)

46. Current long term medications (e.g. oral steroids, other anti-virals, anti-depressants, anxiolytics, HRT or oral contraceptives) Yes ☐ No ☐ *If yes, please give details below*

Name of Medication	Dose	Schedule

47. Drug trial participation Yes ☐ No ☐ If yes, details

48. Other treatments recorded Yes ☐ No ☐ *If yes, give details below*

- ☐ Homeopathy
- ☐ Herbal remedies
- ☐ Chinese medicines
- ☐ Indian medicines
- ☐ Acupuncture
- ☐ Aromatherapy
- ☐ Reflexology
- ☐ Other (please specify)

Section 6. Comments/Notes

Thank you very much for your help.
All the information you provide will be treated in confidence.

Please return this form to:
Aline Brennan, HSE - Health Protection Surveillance Centre, 25-27 Middle Gardiner Street, Dublin 1. Tel: 01 8765300

V 1.1 Jan 2005

Appendix H: Fibrosis scoring systems

Table 46. Comparison of the main liver biopsy fibrosis scoring systems

Score	Original HAI or Knodell	Modified HAI or Modified Knodell or Ishak or Desmet	Scheuer	International group of Hepatopathologists*	Scoring system described in NEJM 1999 paper by Irish Hepatology Research Group
0	No fibrosis	No fibrosis	None	No fibrosis	No fibrosis
1	Fibrosis portal expansion	Fibrosis expansion of some portal areas, with or without short fibrous septa	Enlarged, fibrotic portal tracts	Fibrous portal expansion	Periportal or portal fibrosis
2		Fibrosis expansion of most portal areas, with or without short fibrous septa	Periportal or portal-portal septa with intact architecture	Portal septa with normal vascular relationships	Portal-Portal bridging
3	Bridging fibrosis (portal-portal or portal-central linkage)	Fibrosis expansion of most portal areas, with occasional portal to portal bridging	Fibrosis with architectural distortion but no obvious cirrhosis	Distorted structure or incomplete cirrhosis (focal nodules)	Portal-Central bridging with or without early nodule formation
4	Cirrhosis	Fibrosis expansion of portal areas, with marked bridging (portal to portal as well as portal to central)	Probable or definite cirrhosis	Cirrhosis, probable or definite	Probable or definite cirrhosis
5		Marked bridging with occasional nodules (incomplete cirrhosis)			
6		Cirrhosis, probable or definite			

*Personal communication: Dr Grace Callagy, consultant pathologist in UCHG

Appendix I: Contact Information

Support Groups

Positive Action
56 Fitzwilliam Square, Dublin 2
Tel: 01-676 2853, Fax: 01-662 0009

Transfusion Positive
3 Clanwilliam Square, Dublin 2
Tel: 01-639 8855, Fax: 01-639 8856

Irish Haemophilia Society
First Floor, Cathedral Court, New St, Dublin 8.
Tel:01-657 9900, Fax: 01-657 9901, Email: info@haemophilia.ie
Website: www.haemophilia-society.ie

Irish Kidney Association
Donor House, Block 43a Park West, Dublin 12
Tel: 01-620 5306, Fax: 01-620 5366, Locall: 1890-543 639, E-mail:info@ika.ie
Website: www.ika.ie

Specialist Centres

Beaumont Hospital, Hepatology Unit, Beaumont Road, Dublin 9
Tel: 01-809 2220/01-809 3000

Mater Misericordiae University Hospital, Hepatology Unit, 55 Eccles St., Dublin 7
Tel:01-803 2048/01-803 2000

St. James's Hospital, Hepatology Unit, James's St., Dublin 8
Tel: 01-410 3417/01-410 3000

St. Vincent's University Hospital, Hepatology Unit, Elm Park, Dublin 4
Tel: 01-209 4248/01-269 4533

Our Lady's Children's Hospital, Hepatology Unit, Crumlin, Dublin 12
Tel: 01-409 6742/01-409 6100

Cork University Hospital, Hepatology Unit, Wilton, Cork
Tel: 021 492 2274/021-454 6400

University College Hospital, Hepatology Unit, Newcastle Road, Galway
Tel: 091-544 370/091-524 222

St. Luke's Hospital, Hepatology Unit, Kilkenny
Tel: 056-778 5329/056-778 5000

Liaison Officers

HSE Dublin/North East

Dublin NW/N/N Central
Mr Larry Bathe, Health Service Executive, Northern Area, Primary Care Unit, Rathdown Road, Dublin 7. Tel: 01-882 5003

Cavan, Louth, Meath and Monaghan
Ms Barbara Leech, Health Service Executive, Primary Care Unit, Railway Street, Navan, Co Meath. Tel: 046 907 6451

HSE Dublin/Mid Leinster

Dublin SW/W/S/Kildare Wicklow
Ms Anne Tiernan/Ms Valerie Whelan, Health Service Executive, Primary Care Unit, Block E, Westland Park, Nangor Road, Dublin 22. Tel: 01 460 9671

Dublin SE/Dun Laoghaire/Bray/Wicklow
Ms Carmel Donohoe/John Fennell, Health Service Executive, Civic Centre, Main Street, Bray, Co Wicklow. Tel: 01 274 4291

Laois, Longford, Offaly, Westmeath
Ms Elaine Barry, Primary Care Unit, Health Service Executive, St Loman's, Springfield, Mullingar, Co Westmeath. Tel: 044 938 4429

HSE West

Clare/Limerick/Tipperary North
Mr Michael Griffin, Primary Care Unit Manager, Health Service Executive, Ballycumin Avenue, Raheen Business Park, Limerick. Tel: 061 464 004

Leitrim/Sligo/Donegal
Ms Phil Mulligan/Sadie Flanagan, Community Care Service, Health Service Executive, Iona Office Block, Main Street, Ballyshannon, Co Donegal. Tel: 071 9834000

Galway/Mayo/Roscommon
Ms Catherine Cunningham, Health Service Executive Executive, Merlin Park Regional Hospital, Galway. Tel: 091-775 416

HSE South

Carlow/Kilkenny/Tipperary South/Waterford/Wexford
Mr Cathal O'Reilly/Ms Breda Aylward, Health Service Executive, Lacken, Dublin Rd, Kilkenny. Tel: 056-778 4113

Cork/Kerry
Mr Donal Murphy, Primary Care Unit, 26/27 South Mall, Cork. Tel: 021 492-1872/ 021-492 1871

For all queries that cannot be resolved at local level and within the hospital services:
Ms Michele Tait, Health Service Executive, Mill Lane, Palmerstown, Dublin 20
Tel: 01 620 1750

Relevant National Agencies

Health Protection Surveillance Centre,
25-27 Middle Gardiner St,
Dublin 1.
Tel: 01-8765300
Email: hcvdatabase@hpsc.ie
Website: www.hpsc.ie
Database website: www.hcvdatabase.ie

National Centre for Hereditary Coagulation Disorders (NCHCD)
St James's Hospital, James's St., Dublin 8.
Tel: 01-416 2141

Irish Blood Transfusion Service
National Blood Centre, James's St., Dublin 8
Tel: 01-432 2800

National Virus Reference Laboratory
UCD, Belfield, Dublin 4
Tel: 01-716 1323

Consultative Council on Hepatitis C
2nd floor HSE Offices, Mill Lane, Palmerstown, Dublin 20
Tel: 01-620 1708
E-mail: cchepc@health.irlgov.ie
Website: www.cchepc.ie

Appendix J: Additional tables with detailed statistical results

PCR status

Table 47. Odds ratio for PCR status (ever PCR positive compared to never PCR positive) for each source of infection compared to anti-D (n=1180)

Source of infection and PCR status	Odds ratio	P-value	95% Confidence interval
Anti-D	1	Reference	Reference
Blood transfusion	3.38	<0.001	2.45-4.66
Blood clotting disorders	3.36	<0.001	2.06-5.49
Renal	20.89	0.003	2.81-155.2

Male sex was significantly associated with being PCR positive and may explain the higher odds of being PCR positive in blood transfusion patients and blood clotting disorder patients compared to anti-D patients (who were all female). Age at infection was not associated with PCR status. Even looking only at patients who were confirmed positive (PCR or RIBA positive), the blood transfusion group had significantly higher odds of being PCR positive than the anti-D group.

Alcohol

Table 48. Odds ratio for alcohol in excess of recommended limits for females compared to males (n=1027)

Sex and alcohol consumption in excess of recommended limits	Odds Ratio	P-value	95% Confidence interval
Male	1	Reference	Reference
Female	0.16	<0.001	0.10-0.23

Patients with no information about alcohol intake in their charts were assumed to not consume alcohol in excess of recommended amounts

Liver function tests

Table 49. Multivariate logistic regression analysis of factors associated with abnormally high ALT levels (n=1161)

Factors associated with abnormally high ALT levels	Odds ratio	P-value	95% Confidence interval
PCR status			
No positive PCR results in chart	1	Reference	Reference
Ever tested PCR positive	10.71	<0.001	7.27-15.76
Duration of infection at test			
0-24 years	1	Reference	Reference
25-45 years	2.17	<0.001	1.58-2.97
Cirrhosis			
No	1	Reference	Reference
Yes	1.67	0.053	0.99-2.81
Sex			
Male	1	Reference	Reference
Female	0.41	<0.001	0.29-0.59

Table 50. Multivariate logistic regression analysis of factors associated with abnormally high GGT levels (n=1162)

Factors associated with abnormally high GGT levels	Odds ratio	P-value	95% Confidence interval
PCR status			
No positive PCR results in chart	1	Reference	Reference
Ever tested PCR positive	3.50	<0.001	2.54-4.81
Alcohol			
Within recommended limits	1	Reference	Reference
> recommended limits	2.41	<0.001	1.54-3.77
Cirrhosis			
No	1	Reference	Reference
Yes	3.39	<0.001	1.96-5.84
Sex			
Male	1	Reference	Reference
Female	0.48	<0.001	0.34-0.66

Table 51. Multivariate logistic regression analysis of factors associated with abnormally high AFP levels (n=1003)

Factors associated with elevated AFP levels	Odds ratio	P-value	95% Confidence interval
PCR status			
No positive PCR results in chart	1	Reference	Reference
Ever tested PCR positive	1.95	0.017	1.12-3.39
Cirrhosis			
No	1	Reference	Reference
Yes	6.79	< 0.001	3.89-11.84
Sex			
Male	1	Reference	Reference
Female	0.64	0.07	0.39, 1.04
Duration of infection at test			
0-24 years	1	Reference	Reference
25-45 years	1.70	0.021	1.08-2.66

Liver biopsies

Table 52. Multivariate logistic regression analysis of factors associated with moderate/severe inflammation compared to normal/mild inflammation on last biopsy (n=723)

Factors associated with moderate or severe inflammation on biopsy	Odds ratio	P-value	95% Confidence interval
PCR status			
No positive PCR results in chart	1	Reference	Reference
Ever tested PCR positive	11.01	0.001	2.65-45.82
Alcohol			
Within recommended limits	1	Reference	Reference
> recommended limits	1.95	0.031	1.06-3.56
Duration of infection at last biopsy			
0-24	1	Reference	Reference
25-43	1.61	0.038	1.03-2.52
Age at last biopsy			
6-49	1	Reference	Reference
50-82	1.62	0.026	1.06-2.47
Source of infection			
Anti-D	1	Reference	Reference
Blood transfusion	1.97	0.002	1.28-3.05
Blood clotting disorder	0.95	0.922	0.33-2.71
Renal	1.6	0.427	0.50-5.13

We looked at the influence of male sex and age at infection (30+ years compared to <30) on moderate or severe inflammation on last biopsy. Males were more likely to have moderate or severe inflammation, but it was difficult to separate out the effects of source and sex, and source fits the model better. Older age at infection is associated with moderate or severe inflammation on last biopsy, but the combination of age at last biopsy and duration of infection fit the model better.

Table 53. Multivariate logistic regression analysis of factors associated with fibrosis scores of 4-6 compared to 0-3 on biopsies scored using 0-6 systems (n=542)

Factors associated with fibrosis scores of 4-6 on biopsy	Odds ratio	P-value	95% Confidence interval
Duration of infection at last biopsy			
0-24 years	1	Reference	Reference
25-43 years	1.99	0.024	1.09-3.63
Age at infection			
0-29	1	Reference	Reference
30-77	2.06	0.009	1.20-3.55
Alcohol			
Within recommended limits	1	Reference	Reference
>recommended limits	4.72	<0.001	2.43-9.19
Source of infection			
Anti-D	1	Reference	Reference
Blood transfusion	3.61	<0.001	2.05-6.35
Blood clotting disorder	1.87	0.253	0.64-5.43
Renal	4.35	0.045	1.03-18.3

We looked at the influence of PCR status, male sex and age at last biopsy (50+ years compared to <50) on higher fibrosis scores on biopsy. The number of patients with no positive PCR results biopsied was probably too low to detect an effect (n=80) for PCR status. Males were more likely to have high fibrosis scores, but it is difficult to separate out the effects of source and sex, and source fits the model better. Age at last biopsy was also associated with higher fibrosis scores, but the combination of age at infection and duration of infection fit the model better.

Table 54. Multivariate logistic regression analysis of factors associated with cirrhosis (n=1185)

Factors associated with cirrhosis	Odds ratio	P-value	95% Confidence interval
PCR status			
No positive PCR results in chart	1	Reference	Reference
Ever tested PCR positive	17.96	<0.001	4.34-74.33
Alcohol			
Within recommended limits	1	Reference	Reference
> recommended limits	3.63	<0.001	1.96-6.73
Age at last visit			
10-59	1	Reference	Reference
60-87	1.96	0.013	1.15-3.34
Source of infection			
Anti-D	1	Reference	Reference
Blood transfusion	2.42	0.002	1.39-4.20
Blood clotting disorder	1.03	0.945	0.41-2.59
Renal	1.32	0.723	0.29-6.10

We looked at the influence of male sex, age at infection (30+ years compared to <30) and duration of infection at last visit to unit (30+ years compared to <30) on odds of cirrhosis. All of these were significant on univariate analysis, but no longer significant in the multivariate analysis.

Mortality

Table 55. Cox multivariate regression analysis of factors associated with all-cause mortality for patients with durations of infection up and including 30 years (n=961)

Factors associated with mortality rate	Hazard ratio	P-value	95% Confidence interval
PCR status			
No positive PCR results in chart	1	Reference	Reference
Ever tested PCR positive	1.73	0.056	0.99-3.04
Alcohol			
Within recommended limits	1	Reference	Reference
> recommended limits*	2.11	0.012	1.18-3.79
Sex			
Male	1	Reference	Reference
Female	0.17	<0.001	0.09-0.31
Age at infection			
0-19	1	Reference	Reference
20-34	4.58	0.006	1.54-13.61
35-77	16.1	<0.001	5.47-47.42
Smoking status			
Non smoker	1	Reference	Reference
Smoker	2.3	0.001	1.43-3.69

PCR status is only borderline significant in this model, but does significantly improve the model P=0.04 compared to a model excluding it

Anti-viral treatment

Table 56. Multivariate logistic regression analysis of factors associated with receiving anti-viral treatment for hepatitis C (n=704) (PCR positive patients only)

Factors associated with undergoing anti-viral treatment	Odds ratio	P-value	95% Confidence interval
Hepatitis C Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	4.05	0.001	1.83-8.94
Genotype 3	5.01	<0.001	3.12-8.03
Genotype 5	1.99	0.631	0.12-32.82
Source of infection			
Anti-D	1	Reference	Reference
Blood transfusion	1.49	0.046	1.01-2.20
Blood clotting disorders	1.99	0.021	1.11-3.57
Renal	0.1	0.004	0.02-0.48
Age at last visit			
10-49	1	Reference	Reference
50-87	0.53	0.001	0.36-0.77

Males were significantly more likely to undergoing treatment when included in a model with genotype. However, it is difficult to separate out the effects of source of infection and sex and source fits the model better.

Table 57. Multivariate logistic regression analysis of factors associated with SVR on first treatment (n=250)

Factors associated with sustained virological response	Odds ratio	P-value	95% Confidence interval
Hepatitis C genotype			
Genotype 1	1	Reference	Reference
Genotype 2 or 3	5.73	<0.001	2.44-13.46
Type of therapy			
Monotherapy with IFN	1	Reference	Reference
Combination therapy (IFN/Peg-IFN & RBN)	16.29	<0.001	5.80-45.74
ALT levels			
Normal or abnormally low	1	Reference	Reference
Abnormally high	0.04	<0.001	0.01-0.11
Age at treatment (years)			
10-44	1	Reference	Reference
45-72	0.42	0.043	0.18-0.97
Duration of infection at treatment (years)			
0-9	1	Reference	Reference
10-19	0.41	0.091	0.15-1.15
20-43	0.23	0.018	0.07-0.78
Duration of treatment (weeks)			
0-15	1	Reference	Reference
16-23	4.36	0.067	0.90-21.08
24-47	4.12	0.031	1.14-14.85
48+	8.49	0.001	2.37-30.41

Glossary of definitions, terms and abbreviations

Case definition

Case of hepatitis C for the purpose of this database
Any patient with one or more positive test results for hepatitis C, including positive PCR, RIBA or EIA results, indeterminate RIBA results and weak positive EIA results.

Confirmed positive case of hepatitis C
Any patient who had at least one positive PCR result or at least one positive RIBA result.

Ever hepatitis C PCR positive
Any patient who had at least one positive PCR result.

Definition of alcohol use in excess of recommended limits

More than 14 units (standard drinks) per week for females
More than 21 units (standard drinks) per week for males

A standard drink in Ireland today equals 10gms of alcohol and is equal to a half pint of beer or a single measure of spirits or a small glass of wine. The limits of 14 and 21 standard drinks (spread out over the week) for women and men respectively are used as a general guide for low risk drinking (Strategic Task Force on Alcohol. Second Report. Sept 2004).

Terms

Anti-D
Antibodies against rhesus D antigens. A small amount of the baby's blood can enter the mother's circulation during pregnancy, or larger amounts can enter during delivery. If the mother is negative for rhesus proteins and the baby is rhesus positive, the mother produces antibodies against the rhesus D antigens. These antibodies can pass through the placenta and damage the baby. The risk of disease is higher with subsequent pregnancies with rhesus positive babies. Anti-D immunoglobulin given during or after pregnancy prevents this.

Ascites
The accumulation of fluid in the spaces between tissues and organs in the abdominal cavity.

Autoantibody tests
Autoantibody tests detect antibodies, which normally fight infections and other foreign substance within the body, but are mistakenly attacking the body's own cells, tissues or organs.

Blood clotting disorders (as used in this report)
Inherited blood disorders in which there is a defect in a factor essential for the clotting mechanism of the blood. These include haemophilia A (deficient in factor VIII), haemophilia B (deficient in factor IX), von Willebrand's disease (deficient in von Willebrand factor) and deficiencies of factors V, VII or X.

Cirrhosis
Widespread replacement of liver tissue by fibrotic scar tissue and regenerative nodules, leading to progressive loss of liver function.

Complementary and alternative medicine
A group of diverse medical and health care systems, practices and products that are not presently considered to be part of conventional medicine. The term includes herbalism, aromatherapy, homeopathy, acupuncture, massage and reflexology. Complementary medicine is used together with conventional medicine. Alternative medicine is used in place of conventional medicine.

Confidence interval for an odds ratio
The width of a confidence interval provides a range of plausible values for the odds ratio in the population from which the data were sampled and gives an idea of the degree of confidence about the accuracy of an odds ratio.

Database
A systematically arranged collection of computer data, structured so that it can be automatically retrieved or manipulated.

Extrahepatic manifestations of hepatitis C
Outside of, or unrelated to, the liver. Extrahepatic manifestations associated with hepatitis C include cryoglogulinaemia syndrome, glomerulonephritis, neuropathy, lymphoma, Sjögren syndrome, porphyria cutanea tarda, diabetes.

Fibrosis
Liver fibrosis refers to the accumulation of tough fibrous scar tissue in the liver.

Genotype testing
Hepatitis C genotype tests are used to determine which of the genetically distinct types of hepatitis C virus are present in the patient's blood. Hepatitis C genotype is important in predicting response to anti-viral therapy.

Health Amendment Act (HAA) card
The HAA card is given to people who contracted hepatitis C from the administration within the state of blood or blood products. They are entitled to a range of services under the Health (Amendment) Act 1996.

Hepatic encephalopathy
Neuropsychiatric abnormality in the setting of liver failure. It is caused by toxic substances, which are normally removed by the liver, travelling in the blood to the brain.

Hepatitis C EIA (Enzyme Immunoassay) /ELISA (Enzyme-Linked Immunosorbent Assay)
An assay that detects antibodies against specific hepatitis C antigens in a patient's blood. The hepatitis C EIA test is usually used as an initial screening test for hepatitis C antibodies.

Hepatitis C PCR test (Polymerase Chain Reaction)
Test used to detect the presence of hepatitis C virus RNA (genetic material). A positive PCR result indicates an active infection with replicating virus.

Hepatocellular carcinoma (HCC)
Primary malignancy (cancer) of the liver.

Hepatomegaly
Enlarged liver.

Liver biopsy
A liver biopsy is a medical procedure involving the removal of a small piece of liver using a special needle. This is then examined under a microscope for signs of liver abnormality.

Liver function tests (LFTs)
Liver function tests are a group of blood tests which provide information about how the patient's liver is functioning and may act as indicators of liver injury.

Mean (average)
The mean is a measure of central value that is used when values are normally distributed. The mean is calculated by dividing the sum of all the observations by the total number of observations.

Median
The median is a measure of central value that is used when values are not normally distributed (skewed to one side). The median is obtained by arranging observations from lowest value to highest value and picking the middle value (divides the observations in half).

Meta-analysis
A meta-analysis combines the result of several studies on a particular topic to give an overall summary measure of effect.

Multivariate logistic regression
Logistic regression is used to determine if the presence of, or level of, other characteristics affect the likelihood of a specific outcome of interest occurring. In a multivariate logistic regression model, each factor in the model is adjusted for the effect of the other factors on the outcome.

Odds ratio
The odds ratio is a measure of the odds of an event occurring in one group divided by the odds of it occurring in another group. An odds ratio of 1 indicates that the event is equally likely in both groups.

Oesophageal varices
Abnormally dilated and lengthened sub-mucosal veins in the oesophagus. These are usually a consequence of portal hypertension and may bleed.

Portal hypertension
High blood pressure in the portal vein that carries blood from the digestive tract to the liver. The most common cause is cirrhosis. Consequences can include ascites, hepatic encephalopathy, oesophageal varices and splenomegaly.

Positive predictive value
This is the proportion of all those who test positive who really have the disease or condition.

P-value
In statistics, a result is deemed significant if it is unlikely to have occurred by chance. The p-value is the probability of obtaining a result at least as extreme as the result obtained in the analysis, by chance alone. A p-value of 0.05 indicates that there was a 5% (or 1 in 20) chance of obtaining the result by chance alone. If you are comparing the occurrence of a characteristic in two groups, a low p-value (<0.05) indicates that it is likely that there is a true difference in the value of, or odds of the occurrence of a characteristic in the two groups.

Recombinant immunoblot assay (RIBA)
An additional test for hepatitis C specific antigens in a patient's blood. RIBA tests are usually performed after a positive EIA result and are used to confirm the presence of antibodies to the hepatitis C virus. A positive RIBA result is generally considered confirmation that a patient has been infected with hepatitis C, but cannot differentiate between past infection and current infection.

Renal
The term renal refers to the kidney.

Sensitivity
This measures how often a test turns out positive when it is being used on people who have the disease or condition.

Sicca/ Sjögren's syndrome
A chronic inflammatory disease that is characterized by dryness of mucous membranes especially of the eyes and mouth and by infiltration of the affected tissues by immune cells. There is a strong epidemiological association between Sjögren's syndrome and hepatitis C infection.

Specificity
This measures how often a test turns out negative when it is being used on people who do not have the disease or condition.

Splenomegaly
Enlarged spleen.

Sustained virological response
The absence of detectable hepatitis C RNA in the serum as shown by a qualitative hepatitis C RNA assay with lower limit of detection of 50 IU/ml or less at 24 weeks after the end of treatment.

Abbreviations

AFP	Alpha-fetoprotein (used as a tumour marker for HCC)
ALT	Alanine aminotransferase (a liver enzyme)
Anti-HCV	Antibody to hepatitis C virus
AST	Aspartate aminotransferase (a liver enzyme)
BTSB	Blood Transfusion Service Board, now known as the Irish Blood Transfusion Service
DoHC	Department of Health and Children
EIA	Enzyme immunoassay, a screening test for hepatitis C
GGT	Gamma glutamyl transpeptidase (a liver function test)
HAA	Health (Amendment) Act
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HPSC	Health Protection Surveillance Centre, formerly known as the National Disease Surveillance Centre
HSE	Health Service Executive
IBTS	Irish Blood Transfusion Service, formerly known as the Blood Transfusion Service Board
IFN	Interferon
NDSC	National Disease Surveillance Centre, now known as the Health Protection Surveillance Centre
NICE	National Institute for Clinical Excellence
PCR	Polymerase chain reaction
Peg-IFN	Pegylated interferon
RBN	Ribavirin
RIBA	Recombinant immunoblot assay, a more specific hepatitis C test
RNA	Ribonucleic acid
WHO	World Health Organization

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Health Protection Surveillance Centre
25-27 Middle Gardiner Street Dublin 1 Ireland
Tel: +353 1 876 5300 Fax: +353 1 856 1299
Email: info@hpsc.ie www.hpsc.ie