National Hepatitis C Database

for infection acquired through blood and blood products

HCV
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Follow Up Report 2009

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

hpsc

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Health Protection Surveillance Centre
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HPSC National Hepatitis C Database Team

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Hepatology Units

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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 is a major cause of illness and death, with an estimated 170 million people chronically infected worldwide. Although hepatitis C is not a new disease, the hepatitis C virus was first identified in 1989 so many aspects of its natural history remain to be clarified. Between 50 and 85% of people infected develop chronic infection. A significant proportion develop progressive fibrosis which can lead to liver failure, cirrhosis and hepatocellular carcinoma, usually several decades after infection. However, with the advent of new drug therapies, the disease can now be treated successfully in many people.

Approximately 1,700 people were infected with hepatitis C through receipt 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. On the recommendation of the Consultative Council on Hepatitis C, a database was set up to gather important information on an ongoing basis on this group of people. The fact that most of these people have a known date of infection and are being regularly followed up through a small number of specialist services provides a unique opportunity to carry out research into the natural history of hepatitis C and its treatment. Information collected through the database will also facilitate planning and evaluation of health services.

Baseline data collection took place in 2005 and 2006 and a report on these data was published in 2007. The first round of follow-up data collection was then carried out in 2007 and this report describes the main findings from these data.

Main Findings

- The total number in the eligible population was 1,706. The database cohort at first follow-up period was 1,275 (74.7% of those eligible) and comprised those who consented and those who had died.
- Eighty five people have been added to the database since the baseline data collection, including some who had newly consented and some people newly identified as eligible. Fifty recipients of blood clotting factors, who had been excluded at baseline data collection as they had died prior to the establishment of the designated hepatology units, have now been included in the database.
- Database participation varied with age and sex, with older people and females more likely to participate. People infected through blood clotting factors were also significantly less likely to participate.
- Sixty two per cent (n=787) of database participants were infected through contaminated anti-D. Seventeen are new to the database since baseline. This group is entirely female and their median age at infection was 28 years. Eighty per cent have now been infected for 25 years or longer, the median duration of infection being 29 years.
- Twenty six percent (n=325) of participants were infected either through receipt of contaminated blood transfusions or through treatment for renal disease. Eighteen are new

to the database since baseline. Their median age at infection was 33 years but this ranged from 0 to 77 years. Sixty per cent are female and forty per cent are male. Thirty four per cent have now been infected for 25 years or longer, the median duration of infection being 21 years.

- Twelve per cent (n=157) of participants were infected through contaminated blood clotting factors. Fifty are new to the database since baseline. This group is predominantly male (94%). The date of infection is unknown for most but, using the assumptions outlined in chapter 3, the median age at infection is estimated to be 13.5 years. Fifty three per cent have now been infected for 25 years or longer, the median duration of infection being 25 years.
- Overall, 62% had tested RNA (PCR) positive (indicating active infection) at least once, and a further 15% had positive hepatitis C confirmatory tests but no positive RNA tests. The remaining 23% tested either ELISA/EIA positive/weak positive (a screening test) or RIBA/INNO-LIA indeterminate.
- The overall viral clearance rate at the time of diagnosis was 36% - this varied by sex, 41% for females and 15% for males. However some participants did not have positive confirmatory tests for hepatitis C, so this may be an overestimate of spontaneous viral clearance.
- Of those who were tested for genotype (n=747), 76% were genotype 1, 19% were genotype 3 and 5% were genotype 2. Ninety per cent of the anti-D group were genotype 1.
- Information about alcohol intake was infrequently recorded except at the first visit. Excess alcohol consumption was recorded for 13.6% database participants who ever tested RNA positive; 33% of males exceeded the recommended limits compared to 7% of females.
- Most participants had medical conditions, other than hepatitis C and their index condition (e.g. haemophilia), recorded in their charts. These conditions are not necessarily diagnosed according to standardised criteria and may be unrelated to hepatitis C. The most commonly recorded conditions were fatigue/lethargy (31%), depression (27%) and arthralgia/joint pain (24%). Of these three, only depression was significantly more common in those who were RNA positive (32%) than in those who were never RNA positive (21%). Without a comparison group, it is not possible to determine if the prevalence of these conditions is different from the general population. However, the findings may stimulate interest and prompt further studies.
- ALT (liver enzyme) was elevated in 55% of ever RNA positive participants compared to 10% with no positive RNA results. Abnormally high ALT levels were also significantly more common in males, participants with cirrhosis and those infected for longer durations.
- Signs of liver disease were recorded in the charts of 11.6%, more commonly in those who were ever RNA positive (17.5%) than in those never RNA positive (1.1%).
- By latest follow-up, 12% (n=93) of ever RNA positive participants had developed cirrhosis. Fifty seven were female (10% of RNA positive females) and 36 were male (18% of RNA positive males). The median duration of infection at the estimated date of cirrhosis was 20.5 years and the median age at cirrhosis was 51 years. Alcohol consumption was the biggest determinant of risk of cirrhosis in RNA positive participants. Other factors associated with a higher risk of developing cirrhosis were male sex, genotype 3, age 60 years or older at latest follow-up, age 35 years or older at infection, being infected for 20 years or longer and infection through blood transfusion.
- Twenty two participants had developed hepatocellular carcinoma (HCC), of whom 16 were known to be deceased. The median duration of infection at the estimated date of HCC was 22 years and the median age at HCC was 66 years.

- Twenty five per cent of ever RNA positive participants who had a liver biopsy had moderate or severe inflammation on the last biopsy; this was higher in the blood transfusion/renal group (33%) than in the anti-D group (21%). Most participants infected through blood clotting factors did not have liver biopsies carried out.
- Seventeen per cent of ever RNA positive participants had a high fibrosis score on the most recent liver biopsy; this figure was 30% for the blood transfusion/renal group, 24% for the clotting factor group and 11% for anti-D participants. Factors associated with having a high fibrosis score include ever testing RNA positive, older age at infection, male sex, high alcohol intake and genotype 3 infection.
- One hundred and seventy three participants had died by latest follow-up. This represents 63 additional deceased participants compared to baseline but 52 of these were new to the database since baseline and most had died many years previously. Where death certificates were available (n=165), death was directly caused by liver disease in 43 participants. Data on alcohol consumption were available for 34 of these, of whom 53% (n=18) had high alcohol consumption. Mortality rates were higher in participants who tested RNA positive, in those with high alcohol consumption, males, HIV co-infection, those who were older at infection and those infected through blood transfusions/ treatment for renal disease or blood clotting factors.
- Almost 40% (n=309) of RNA positive participants had one or more courses of anti-viral treatment by the latest follow-up. Participants with higher fibrosis scores, genotype 2 or 3 and those infected through clotting factors were more likely to have been treated. Treated participants were also younger and infected for shorter durations compared to those who have not yet been treated.
- The factors associated with sustained virological response (SVR) on first treatment were combined therapy rather than monotherapy, longer duration of treatment, having genotype 3 rather than genotype 1, younger age at treatment and shorter duration of infection at treatment. Eighty nine per cent (n=8) of genotype 3 participants on combination therapy for 48 weeks or more achieved an SVR compared to 46% (n=18) of genotype 1 participants on the same treatment. More detail of response rates to different regimes is presented in chapter 4 but the results should be interpreted with caution as the numbers in some treatment categories are small.
- Sixty eight (43%) participants infected through blood clotting factors were also infected with HIV. The database is unlikely to be useful in looking at the natural history of disease progression in these people as 62% (n=42) are now deceased. Most died in the early to mid 1990s and had never had an RNA test. However, 21 (31%) of the co-infected participants had one or more signs of liver disease and 7 (10.3%) had cirrhosis by latest follow-up.
- Fifteen participants had received liver transplants. The median age at transplant was 51 years and the median duration of infection at transplant was 27 years. All transplant recipients were RNA positive when transplanted.
- A summary variable was created to represent more severe hepatitis C disease and logistic regression analysis was used to examine factors associated with it. This showed that the determinants of more severe hepatitis C disease in the database cohort were: high alcohol intake, male sex, older age at infection, longer duration of infection, elevated ALT level and genotype 3.
- Eighty three per cent (n=557) of living RNA positive participants had visited their hepatology unit within two years up to the end of 2007 compared to 61% (n=259) of never RNA positive participants.
- The specialist services, other than hepatology, most commonly attended recently by participants were rheumatology, haematology, physiotherapy, psychiatry, psychology and counselling.

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

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 national hepatitis C database contains a large amount of data on over one thousand people infected with hepatitis C in Ireland. A significant proportion of participants have now been infected for more than 25 years. International literature suggests that chronic hepatitis C disease progresses particularly between 20 and 30 years after infection, so this is now an important time to focus on outcomes and response to treatment through regular follow-up. Information about usage of services will also be helpful in predicting and planning for service needs in the future.

There is now evidence of significant disease progression in a proportion of those participants with chronic long-term infection, with 12% having developed cirrhosis. Apart from RNA status, high alcohol consumption was found to be the most important determinant of risk of cirrhosis and other adverse outcomes. Older age at infection, male sex, longer duration of infection and genotype 3 were also associated with poorer outcomes in database participants. Apart from the association with genotype 3, the other findings are in line with the published literature. The suggestion of poorer outcome for some genotype 3 patients will be followed closely in coming years.

One very important outcome of the database so far has been the information on treatment responses. Although this information has been well published from international studies, the data presented in this report represent the true outcomes in an Irish population. Treatment response in database participants has improved in recent years with the advent of combination therapy and is in line with the international experience, both in terms of the proportion achieving sustained virological response, and in the influence of age, genotype and type of treatment.

In general, the quality of the information in the database is good. However, there are limitations, some of which we hope to improve in the future.

The participation rate already achieved in this project is a tribute to the co-operation and support of the participants, support groups and staff in the hepatology units. It is our aim to continue to improve this rate by encouraging non-responders to join now. A higher participation rate will mean that the data will more closely reflect the entire hepatitis C population infected through blood and blood products in Ireland. For eligible people who would like to participate and have not yet consented, consent forms are available through the hepatology units.

The lack of a population-based comparison group limits the interpretation of some of the data, particularly those related to other medical conditions. A cross-sectional study is being planned to compare health, illness and lifestyle indicators in the hepatitis C database cohort with the general population using questions and data from large-scale standardised health surveys.

The lack of standardisation of data recording in two areas has given rise to difficulties – liver biopsy scoring and viral load measurement. We hope to resolve these issues in the coming year so that optimum use can be made of this information.

We hope to improve recording of data in two other key areas – BMI and alcohol consumption. Both of these factors are known to be key determinants of hepatitis C disease progression. Recent data on both

are essential in accurately assessing their impact so we would encourage clinical staff to attempt to record these at routine out-patient visits.

The data in the database are available for use by researchers and by the participating hepatology units. The annual collection of data on participants will continue. The type of data collected each year may be modified as new questions arise or new developments come to light. Regular reports will be produced with a focus on health outcomes, treatment response and service usage.

Finally, we would welcome any comments and suggestions that participants, health professionals or other interested people may have on ways in which we could improve the database and the use of the information contained in it.

Summary tables

Table 1. Summary of main outcomes by hepatitis C RNA and line-immunoassay (RIBA/INNO-LIA) status for all participants

Outcomes	All participants (%)	Ever RNA positive (%)*	RNA tested and never positive, had positive confirmatory antibody results (%)†	RNA tested and never positive, had no positive confirmatory antibody results (%)‡	No RNA results in chart (%)§
Signs of liver disease	148 (11.6)	137 (17.5)	4 (2.1)	1 (0.4)	6 (12.8)
Cirrhosis	97 (7.6)	93 (11.9)	0	0	4 (8.5)
Liver tumours or HCC	22 (1.7)	20 (2.6)	0	0	2 (4.3)
Ever had high fibrosis score on biopsy ‖	147 (11.5)	141 (18.0)	4 (2.1)	0	2 (4.3)
Deceased	173 (13.6)	116 (14.8)	15 (7.9)	2 (0.8)	40 (85.1)
Liver related disease directly caused death	43 (3.4)	33 (4.2)	2 (1.1)	0	8 (17.0)
All	**1275**	**784**	**190**	**254**	**47**

** At least one positive hepatitis C RNA result*

† Positive line-immunoassy results (RIBA/INNO-LIA), RNA tests done but never tested RNA positive

‡ Strongest result was positive/weak positive EIA/ELISA or indeterminate line-immunoassay result, RNA tests done but never tested RNA positive

§ No RNA results in chart (mostly deceased patients who died before they could be tested)

‖ Fibrosis score of 3 or 4 on biopsy scored from 0 to 4 or fibrosis score of 4, 5 or 6 on biopsy scored from 0 to 6

Table 2. Current RNA status (this includes the last known status of deceased participants) for all participants

Final Status	All participants (%)	Ever RNA positive (%)*	Confirmed positives (%)†
Currently chronically infected‡	605 (47.5)	605 (77.2)	605 (62.0)
Cleared virus without treatment	224 (17.6)	32 (4.1)	224 (23.0)
Treated and cleared virus	147 (11.5)	147 (18.8)	147 (15.0)
Not confirmed positive	299 (23.5)		
All	**1275**	**784**	**976**

**At least one positive hepatitis C RNA result*

† Positive line-immunoassy results (RIBA/INNO-LIA) or positive RNA results

‡ Hepatitis C RNA positive at most recent test (includes participants who have died)

Table 3. Summary of main outcomes by hepatitis C RNA and line-immunoassay (RIBA/INNO-LIA) status for anti-D participants

Outcomes	All participants (%)	Ever RNA positive (%)	RNA tested and never positive, had positive confirmatory antibody results (%)	RNA tested and never positive, had no positive confirmatory antibody results (%)
Signs of liver disease	45 (5.7)	41 (9.8)	2 (1.4)	1 (0.5)
Cirrhosis	31 (3.9)	30 (7.2)	0	0
Liver tumours or HCC	3 (0.4)	3 (0.7)	0	0
Ever had high fibrosis score on biopsy	66 (8.4)	63 (15.1)	2 (1.4)	0
Deceased	38 (4.8)	26 (6.2)	10 (6.9)	1 (0.5)
Liver related disease directly caused death	7 (0.9)	5 (1.2)	1 (0.7)	0
All	**787**	**417**	**146**	**216**

8 anti-D participants had no RNA results in their charts

Table 4. Current RNA status (this includes the last known status of deceased participants) for anti-D participants

Final Status	All participants (%)	Ever RNA positive (%)	Confirmed positives (%)
Currently chronically infected	340 (43.2)	340 (81.5)	340 (60.4)
Cleared virus without treatment	165 (21.0)	19 (4.6)	165 (29.3)
Treated and cleared virus	58 (7.4)	58 (13.9)	58 (10.3)
Not confirmed positive	224 (28.5)		
All	**787**	**417**	**563**

Table 5. Summary of main outcomes by hepatitis C RNA and line-immunoassay (RIBA/INNO-LIA) status for blood transfusion/renal participants

Outcomes	All participants (%)	Ever RNA positive (%)	RNA tested and never positive, had positive confirmatory antibody results (%)	RNA tested and never positive, had no positive confirmatory antibody results (%)
Signs of liver disease	69 (21.2)	67 (25.4)	2 (7.7)	0
Cirrhosis	50 (15.4)	50 (18.9)	0	0
Liver tumours or HCC	13 (4.0)	13 (4.9)	0	0
Ever had high fibrosis score on biopsy	73 (22.5)	70 (26.5)	2 (7.7)	0
Deceased	70 (21.5)	62 (23.5)	5 (19.2)	1 (3.0)
Liver related disease directly caused death	18 (5.5)	17 (6.4)	1 (3.9)	0
All	**325**	**264**	**26**	**33**

2 blood transfusion/renal participants had no RNA results in their charts

Table 6. Current RNA status (this includes the last known status of deceased participants) for blood transfusion/ renal participants

Final Status	All participants (%)	Ever RNA positive (%)	Confirmed positives (%)
Currently chronically infected	194 (59.7)	194 (73.5)	194 (66.7)
Cleared virus without treatment	34 (10.5)	7 (2.7)	34 (11.7)
Treated and cleared virus	63 (19.4)	63 (23.9)	63 (21.7)
Not confirmed positive	34 (10.5)		
All	**325**	**264**	**291**

Table 7. Summary of main outcomes by hepatitis C RNA and line-immunoassay (RIBA/INNO-LIA) status for blood clotting factor participants

Outcomes	All participants (%)	Ever RNA positive (%)	RNA tested and never positive (%)	No RNA results in chart (%)
Signs of liver disease	33 (21.0)	28 (28.0)	0	5 (13.5)
Cirrhosis	15 (9.6)	12 (12)	0	3 (8.1)
Liver tumours or HCC	6 (3.8)	4 (4.0)	0	2 (5.4)
Ever had high fibrosis score on biopsy	8 (5.1)	8 (8.0)	0	0
Deceased	64 (40.8)	27 (27)	0	37 (100)
Liver related disease directly caused death	17 (10.8)	10 (10.0)	0	7 (18.9)
All	**157**	**100**	**20**	**37**

Table 8. Current RNA status (this includes the last known status of deceased participants) for blood clotting factor participants

Final Status	All participants (%)	Ever RNA positive (%)*	Confirmed positives (%)
Currently chronically infected	68 (43.3)	68 (68.0)	68 (57.6)
Cleared virus without treatment	24 (15.3)	6 (6.0)	24 (20.3)
Treated and cleared virus	26 (16.6)	26 (26.0)	26 (22.0)
Not confirmed positive	39 (24.8)		
All	**157**	**100**	**118**

Hepatitis C RNA status and disease outcomes

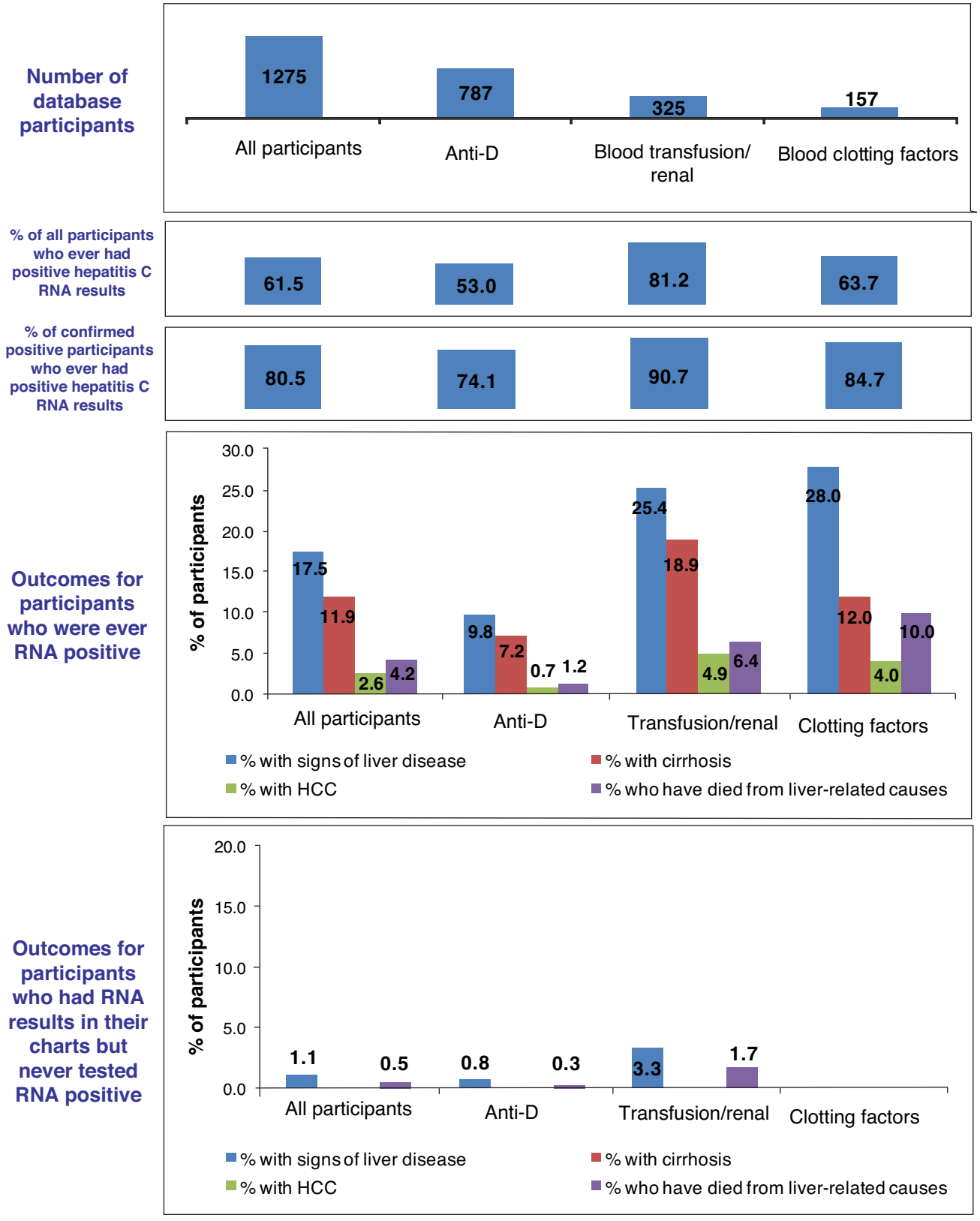

Figure 1. Summary of RNA status, and disease progression by RNA status, for all participants and by source of infection

47 participants had no RNA results in their charts, 37 of these were infected through contaminated blood clotting factors. These participants were similar to the ever RNA positive group in terms of outcomes. Six participants had a source of infection other than those shown.

Chapter 1 Introduction

Hepatitis C

Hepatitis C infection has emerged over the last two decades as a major cause of illness and death worldwide. Between 50 and 85% of people infected with hepatitis C become chronically infected and it is estimated that 170 million people are chronically infected worldwide.[1,2] A significant proportion develop progressive fibrosis which can lead to liver failure, cirrhosis and hepatocellular carcinoma (HCC). Studies have found that after approximately 20 years, 5-20% of those who are chronically infected will have developed cirrhosis.[1] The median time from infection to cirrhosis was estimated to be 30 years in one study[3] and 31 years in another.[4] In those with cirrhosis the annual rate of decompensated liver disease is estimated to be 4% and the annual rate of HCC is estimated to be 1.6%. The annual death rates in industrialised countries from decompensated cirrhosis and HCC are estimated to be 15% and 80%, respectively.[1]

Disease progression has been found to vary depending on patient characteristics. Factors implicated in faster progression include older age at infection, longer duration of infection, higher alcohol consumption,[3,5,6,7,8,9] body mass index (BMI)/steatosis,[4,5] co-infection with human immunodeficiency virus (HIV) or hepatitis B,[5,8] elevated alanine amino transferase (ALT) levels,[4,5,9] and inflammation on biopsy.[5,7,9] Male sex has been associated with a worse prognosis in several studies[3,5,6,8,9] but this association has not been found in others.[4,7] Host human leucocyte antigen (HLA) types have also been found to play a role.[3,10,11,12,13]

Most studies have found that mode of acquisition,[5,7,9] genotype and hepatitis C viral load do not affect disease progression.[5,8] However, genotype is a key determinant of anti-viral treatment outcome, with people infected with genotype 1 hepatitis C having lower sustained virological response (SVR) rates than those infected with genotypes 2 or 3. Treatment response rates have improved significantly for all genotypes since the advent of combination therapy with pegylated interferons and ribavirin. SVR rates of 42-46% for genotype 1 patients, and 76-82% for genotype 2 or 3 patients, have been achieved in large-scale clinical trials.[14] Recent studies have also shown that early virological response is a very good predictor of sustained response, allowing treatment to be discontinued if an early response is not achieved.[15] Alternative or adjunct therapies to interferons and ribavirins may also be available in the near future as new specifically targeted anti-viral therapies for hepatitis C are showing promise in clinical trials.[16]

Background to the database

Approximately 1,700 people were infected with hepatitis C through receipt 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. Specialist hepatology services were set up in eight designated hospitals to provide services for this group. They are also entitled to a range of additional hospital and primary care services under the Health (Amendment) Act, 1996. Many of these people have a known year of infection and a large proportion have now been infected for over 25 years.

In 2000, the Consultative Council on Hepatitis C recommended that a database be developed to follow the natural history of infection and evaluate the impact of host and virus factors on disease progression in this cohort.[17] The Health Protection Surveillance Centre (formerly the NDSC) was given the responsibility of developing the database.

Baseline data were collected in 2005 and 2006 and included all relevant data from the date of diagnosis. A report describing these data was published in October 2007.[18] A patient newsletter was also published in January 2008, summarising the baseline data (appendix C). Both are available through the hepatology units, patient support groups, hepatitis C liaison officers and on the database website (www.hcvdatabase.ie). The first year of follow-up data collection took place in 2007 and is the subject of this report.

Chapter 2 National Hepatitis C Database

The national hepatitis C database for infection acquired through blood and blood products was developed 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). Approval for this project was obtained from the ethics committees of all eight hospitals and from the Office of the Data Protection Commissioner.

The development and management of the database project is overseen by a steering committee (appendix A). A scientific and technical group supports and advices HPSC on the scientific and technical development of the database (appendix B).

The objectives of the database are:

1. To follow the natural history of infection in people infected through blood and blood products
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

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, line-immunoassay (RIBA/INNO-LIA) positive or indeterminate, or hepatitis C polymerase chain reaction (PCR)/RNA positive. Eligible participants 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 people who have died. Relatives of deceased people are entitled to refuse participation and no data are collected on those who refused to participate in the database when they were alive.

Source of data

Information is gathered from the participant's medical records (hospital charts) in the eight hepatology units and is updated on an annual basis. No direct contact is made with any participant. No names or addresses are recorded in the database.

Data security

The database was built using MS SQL server 2000. It is physically located in a secure computer room in HPSC with access strictly limited to key technical support staff. Access to the database is secured by a combination of network, SQL server and MS Access security permissions. All paper forms are stored in a locked cabinet in HPSC.

Chapter 3 Follow-up Data Collection

Data collection

The collection of the first round of follow-up data began in January 2007. The data collection form used for the first year of follow-up is shown in appendix D. A research nurse from HPSC carried out the data extraction in the hepatology units. The follow-up data collected includes all relevant clinical, demographic and lifestyle data identified in the participants' medical records between the date of baseline collection (2005-2006) and the date of follow up data collection (up to 31st December 2007). Data were entered into the database by a surveillance assistant. Double entry was used to maximise accuracy.

Recruitment of new participants

Eligible people who have not yet participated may join the database at any time. These would include those people who did not consent to database participation when first invited to do so in 2004, and those newly identified as eligible since 2004.

The eight hepatology units actively encourage their patients to participate when they attend for routine hospital visits. To facilitate this, consent forms and information leaflets have been placed in the medical charts of those who have not yet responded. Those who initially refused to consent to participate are not asked again. The patient support groups also encourage their members to participate through their newsletters and meetings.

In order to reach eligible participants who may not attend one of the eight hepatology units, a letter was sent in 2008 to the consultants in infectious diseases throughout the country informing them of the purpose of the database and asking for their assistance in recruiting eligible participants who might be attending their services rather than hepatology.

Since the baseline data collection it has come to our attention that some eligible people had died prior to the establishment of the designated hepatology units and thus they were omitted from the study population at baseline. In the main, these were people who were infected through receipt of blood clotting factors. Therefore, in 2008 the hepatology unit in St James's Hospital worked with the National Centre for Hereditary Coagulation Disorders (NCHCD) to identify and include these participants in the database.

There is a small number of people living abroad (approximately 20) who meet the eligibility criteria for the database but who do not attend a clinical service in Ireland. They are not currently included in the database due to the difficulties that would arise in terms of data collection, data quality, confidentiality and consent.

Consent issues for participants reaching adulthood

During baseline data collection, parental consent was required for all eligible participants who were under the age of 18 years. Participants who were aged 16 and 17 years were invited to co-sign the consent form. During follow-up data collection, the consultant hepatologists wrote to the parents of eligible participants who were under the age of 16 years at baseline data collection but who were now 16 or 17 years to offer their child the opportunity to co-sign the consent form. The consultant hepatologists also wrote to those participants who were under the age of 18 years at the time of baseline data collection, but are now 18 years of age or older, to ask them to sign a consent form in their own right.

Assumptions

Various assumptions were made where data were missing. These mainly related to year of infection and are listed below:

- 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/treatment for renal disease: 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. Where the person had also been on dialysis for extended periods of time, the year of starting dialysis or of first blood transfusion, whichever was the earlier, was used as an estimate of the year of infection.
- Clotting factors: For people with haemophilia and other blood clotting disorders, if the year of infection was not available, the year that the patient first received clotting factors was used as a proxy for the year of infection. Where the year of infection and the year when first factor was administered were missing, then the year of diagnosis of haemophilia was used for the year of infection.
- If the patient had multiple potential exposures, tested negative for hepatitis C after one or more exposures and subsequently tested positive, then the date of the first exposure after the last negative test was taken as the date of infection. If there were multiple potential exposure dates between the last negative and first positive results, then the midpoint of the test dates was assigned 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.

Estimating dates of cirrhosis and hepatocellular carcinoma (HCC)/liver cancer

Variables were created to indicate if participants had cirrhosis or liver cancer on biopsy or mentioned elsewhere in their charts or death certificates. Estimated dates of onset were generated for both conditions, but these were approximate. If multiple biopsies, ultrasounds or CT scans were done, the midpoint between the first positive and last negative date was used. Where cirrhosis or liver cancer was first mentioned on death certificates, the midpoint between the date of death and last negative diagnostic test or last visit to the hepatology unit was used. Otherwise the earliest date mentioned in relation to a diagnosis of cirrhosis or liver cancer was used.

Estimating duration of hepatitis C ribonucleic acid (RNA) positivity

All RNA results were recorded for each participant. A variable was created to record the duration of RNA positivity in years for all participants who ever tested positive. The following rules were used:

- If a participant remained RNA positive when last tested and was still alive, the duration of RNA positivity was calculated as their date of last visit minus their date of infection. If they were deceased, their date of death minus their date of infection was used.
- For participants who had tested RNA positive and cleared the virus, the duration of RNA positivity was calculated as the midpoint between the first negative and last positive result minus their date of infection.

Coding of death certificates

Death certificates were collected on deceased participants 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. Analysis was done on the underlying cause of death as defined by the ICD system.
The cause of death 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 hepatocellular carcinoma or end-stage liver disease (varices, ascites, liver failure or hepatic encephalopathy) were listed as any of the causes of death in section I of the death certificate

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,

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 RNA status of the participant.

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.[6]

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.

Liver biopsies

Different scoring systems were used to stage and grade the hepatitis C liver biopsies in the different hepatology units (appendix E):

- Knodell system:[19] fibrosis scored from 0-4
- Modified Knodell system,[20,21] also known as the Ishak or the modified HAI system: fibrosis scored from 0-6
- Scheuer system:[22] fibrosis scored from 0-4
- International Group of Hepatopathologists system: fibrosis scored from 0-4

For some of the analyses, the biopsies scored from 0 to 6 were converted to 0 to 4 scores so that all scored biopsies could be considered together. The following conversions were used: 0=0, 1=1, 2=1, 3=2, 4=3, 5=3 and 6=4.

Data analysis

Data were analysed using Business Objects, Microsoft Access 2007, Microsoft Excel 2007 and Stata/SE version 9.2. The Wald test, with corresponding probability value (P-value) and 95% confidence intervals, was 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

The main findings after the first round of follow-up data collection are presented as follows:

- **Summary of the eligible cohort**
- **Description of database population**
- **Hepatitis C RNA status and genotype**
- **Alcohol consumption**
- **Medical conditions**
- **Liver disease – cirrhosis, inflammation, fibrosis, HCC**
- **Deaths, cumulative survival**
- **Anti-viral treatment**
- **Hepatitis C and HIV co-infection**
- **Summary of determinants of disease progression**
- **Health Service Usage**

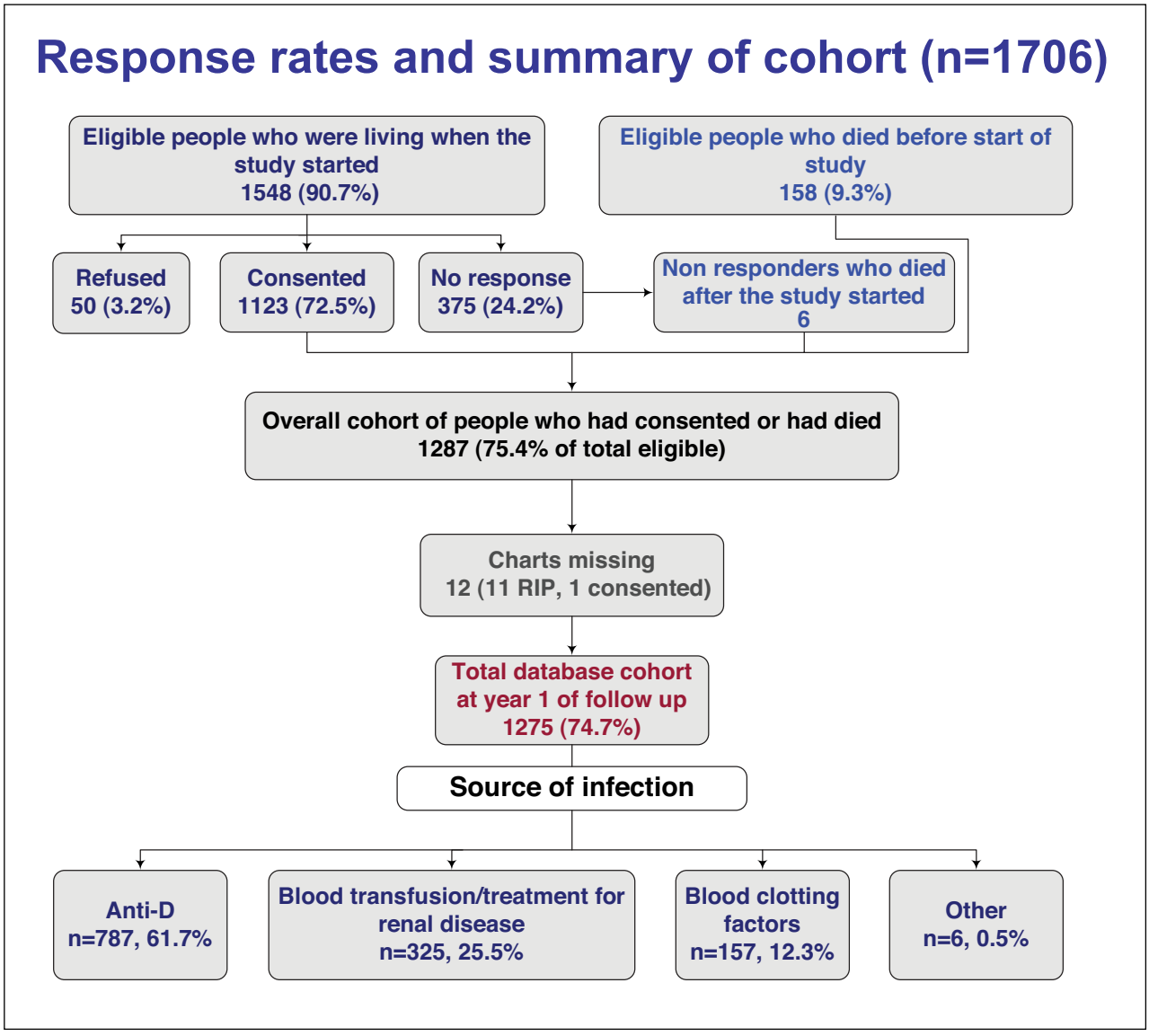

Figure 2. Summary of participation rates and database cohort

(Source of infection = other, includes participants infected through vertical or sexual contact with people with state-acquired infection)

New participants since baseline

Eighty five people have been added to the database since the baseline round of data collection, bringing the total number of participants to 1,275 (two participants were removed since baseline as they were found to be duplicates of other database participants). The new database participants include thirteen new consents, twenty participants newly identified as eligible, two newly deceased participants and fifty participants identified in collaboration with the National Centre for Hereditary Coagulation Disorders (NCHCD) in St James's Hospital. The database participation rate is now 75% and the consent rate is 73% (figure 2).

End of latest follow-up and time between baseline and follow-up data collection

Data up to the end of 2007 were collected for the first year of follow-up, where available. However, latest follow-up for each participant is effectively their last visit to the hepatology unit as this is the last date when information was recorded in their medical charts. Date of death was the date of end of latest follow-up for deceased participants. The baseline data were the last available data for 346 of the baseline participants (29%). One hundred and twelve were deceased and the remainder had not visited their hepatology unit since the baseline data were collected. Of the living participants who had not attended their unit since baseline, 175 were RNA negative on last test and 59 were RNA positive on last test. Of those who were RNA positive, 29% had attended within two years of follow-up data collection, 52% attended within three or four years and 19% had not attended in over five years. Some are likely to have moved abroad and may be lost to follow-up. For participants with both baseline and follow-up data, the median time between the two rounds of data collection was 23 months.

Representativeness

Database participation varied with age and sex, with older people and females more likely to participate, even when only living participants are considered (figure 3). These differences are statistically significant.

People infected through blood clotting factors were also significantly less likely to participate in the database compared to people infected through other means (figure 4). It is not possible to determine if this is due to the predominance of males and younger participants in this group as we only have access to summary data on source of infection and sex for non-participants.

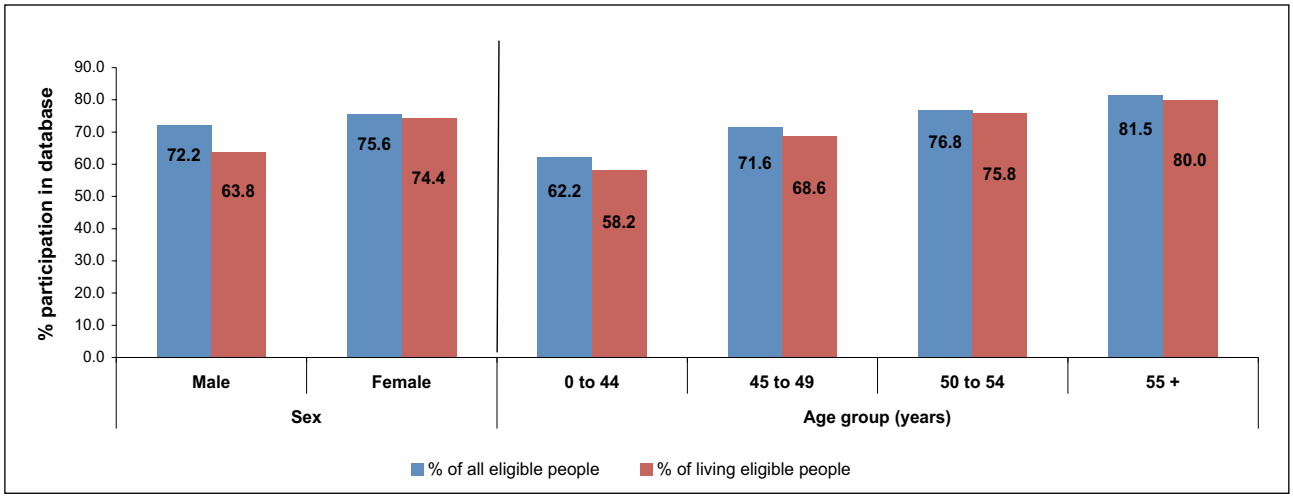

Figure 3. Percentage of eligible people participating in the database by sex and age group at the start of the database project

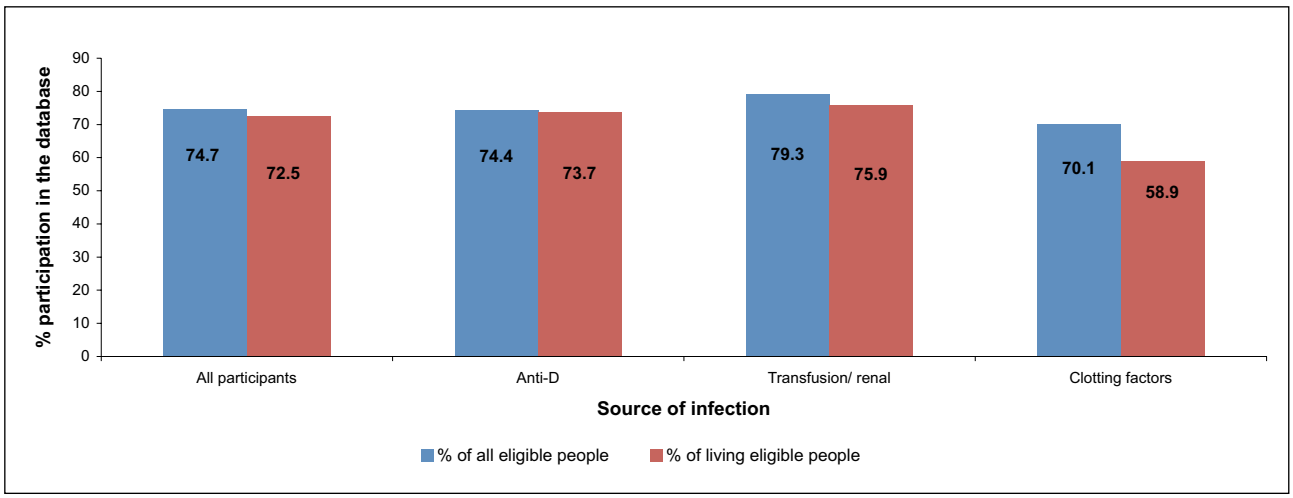

Figure 4. Percentage of eligible people participating in the database by source of infection

Description of database population

Age, sex, source of infection and duration of infection

Participants infected through contaminated anti-D

Sixty two percent (n=787) of database participants were infected through contaminated anti-D (figure 5). Seventeen are new to the database since the baseline report. The anti-D group is entirely composed of females who were infected during their child-bearing years. As a group, they would be expected to have been relatively healthy when infected. The median age at infection for these participants was 28 years.

Infection due to contaminated anti-D has been largely traced to batches of anti-D from two infected donors. Batches from the first donor were contaminated with genotype 1 hepatitis C and were distributed between 1977 and 1979. Eighty five percent (n=665) of anti-D participants were infected during this period. Batches from the second donor were infected with genotype 3 hepatitis C. These were administered between 1991 and 1994 and accounted for ten percent (n=75) of participating anti-D participants. The estimated year of infection for the remaining forty seven participants was outside of these outbreak periods and sixty eight percent (n=32) did not have positive confirmatory results for hepatitis C.

By latest follow-up, eighty percent of the anti-D participants had been infected for 25 years or longer. The median duration of infection was 29 years and the median duration of RNA positivity for those who ever tested positive was also 29 years (figure 6).

Participants infected through contaminated blood transfusions or treatment for renal disease

Twenty six percent (n=325) of participants were infected either through receipt of contaminated blood transfusions or through treatment for renal disease (figure 5). Eighteen are new to the database since the baseline report. This group was the most heterogeneous in terms of age and sex. They had the highest median age at infection (33 years), but this ranged from 0 to 77 years. Sixty percent were female and forty percent were male, making this the only group with sizable proportions of each sex. Using the assumptions outlined in chapter 3, most of the blood transfusion/renal participants were infected in the late 1970s and 1980s. They had the shortest duration of infection at latest follow-up, with 34% infected for 25 years or longer. Their median duration of infection was 21 years and the median duration of RNA positivity for those who ever tested positive was 20 years (figure 7).

Participants infected through contaminated blood clotting factors

Twelve percent (n=157) of participants were infected through contaminated blood clotting factors (figure 5). This group has increased the most since the baseline report, with an additional 50 participants. Participants infected through clotting factors were predominantly male (94%) and 43% were co-infected with human immunodeficiency virus (HIV). Using the assumptions outlined in chapter 3, most were infected as children in the mid-1970s to early 1980s. The median age at infection was 13.5 years. By latest follow-up, 53% had been infected for 25 years or longer. The median duration of infection was 25 years and the median duration of RNA positivity for those who ever tested positive was 27 years (figure 7).

The distributions of age at infection and age at end of latest follow-up for all database participants are shown in figures 8 and 9.

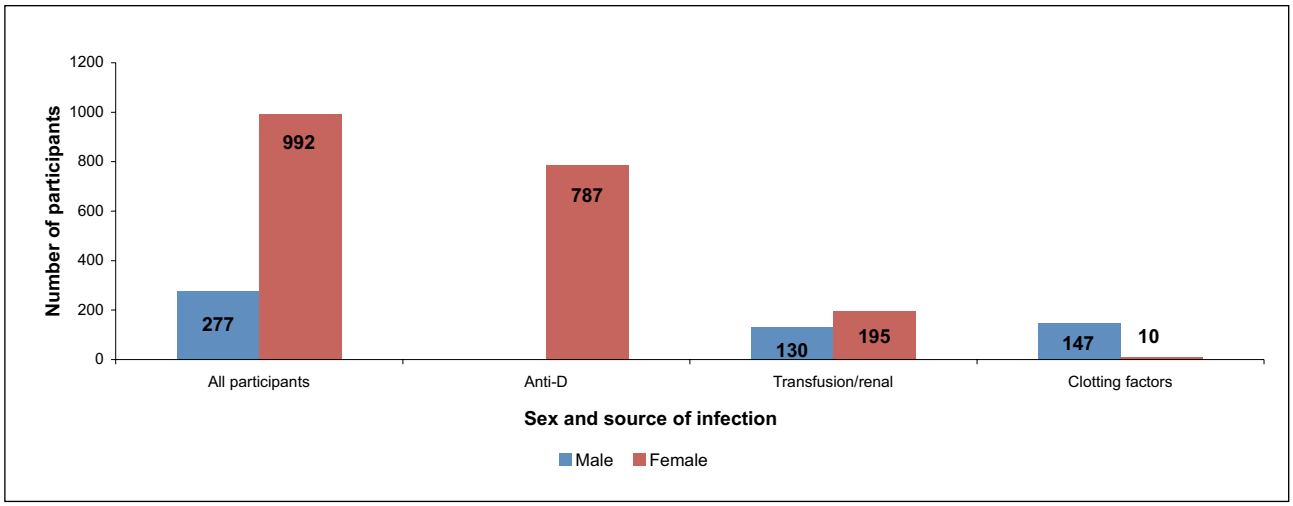

Figure 5. Number of participants by sex and source of infection (6 participants infected through other means omitted)

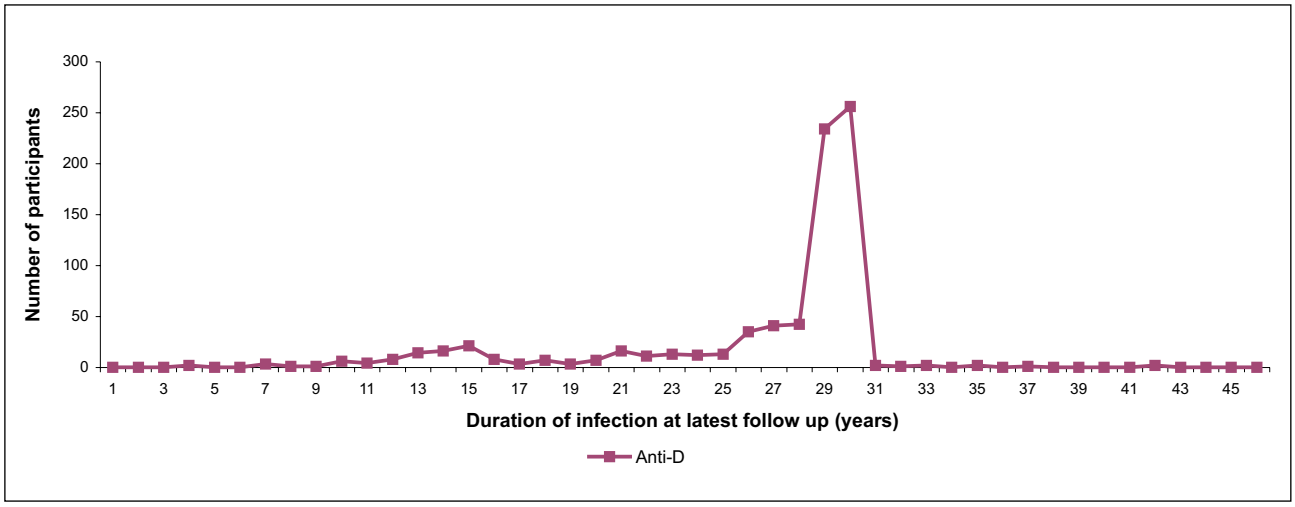

Figure 6. Number of participants by duration of infection at end of latest follow-up for participants infected through anti-D (n=787)

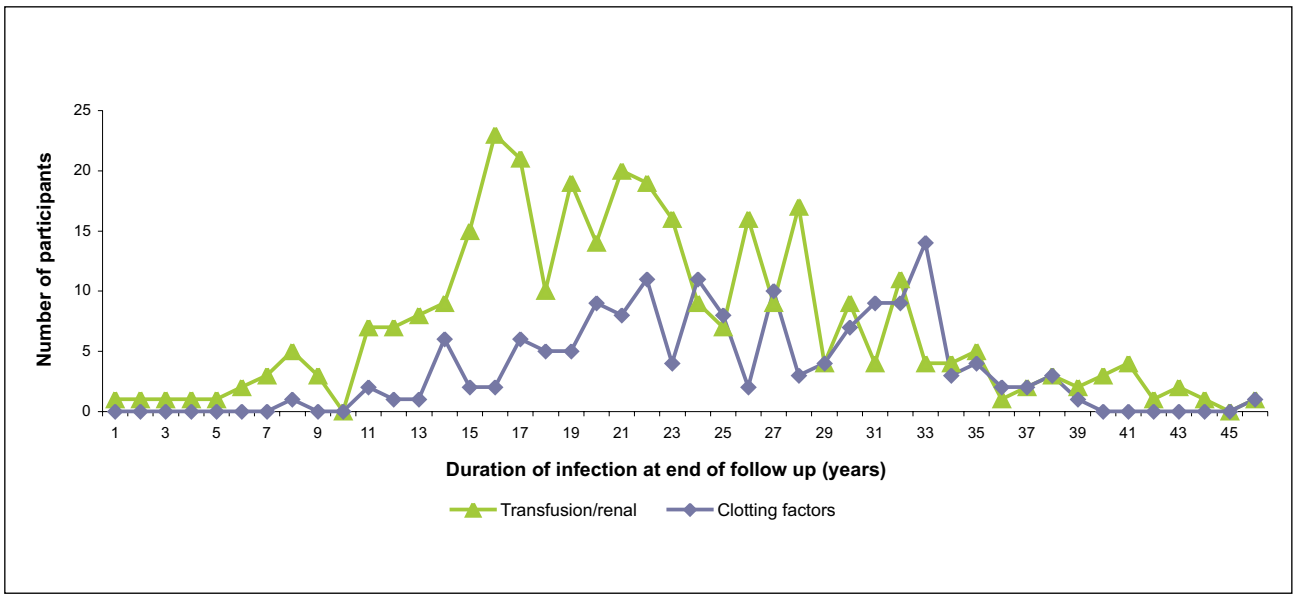

Figure 7. Number of participants by duration of infection at end of latest follow-up for participants infected through blood transfusion/treatment for renal disease (n=325) and blood clotting factors (n=157)

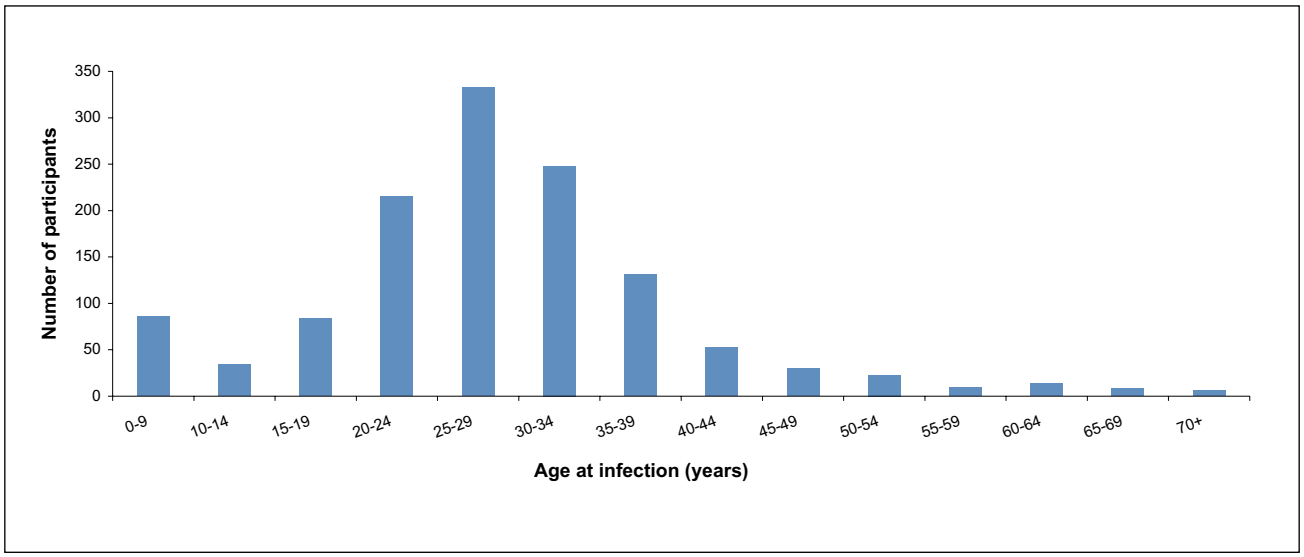

Figure 8. Number of participants by age at infection (n=1273)

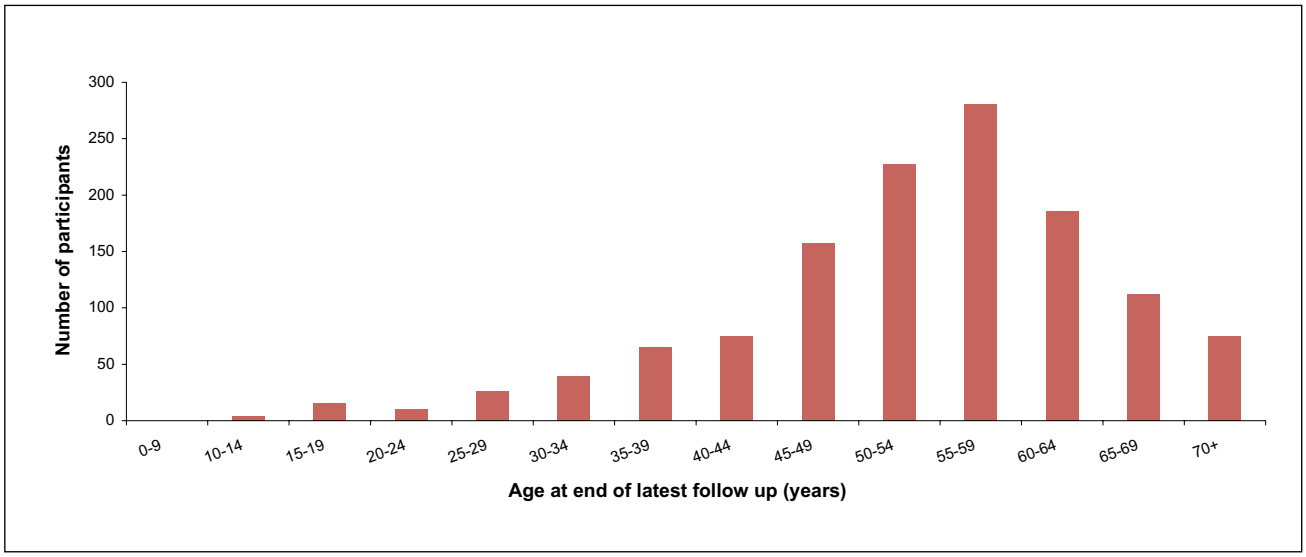

Figure 9. Number of participants by age at end of latest follow-up (n=1275)

RNA results

RNA tests are used to test for circulating virus. Positive results indicate current infection. In general, enzyme-linked immunosorbent assay (ELISA/EIA) tests are used as screening tests for hepatitis C, and line-immunoassay tests (e.g. RIBA/INNO-LIA) are used to confirm positive antibody results. However, people with positive or weak positive ELISA/EIA tests or indeterminate RIBA/INNO-LIA tests were included in the database as many patients were tested many years after suspected infection, had documented exposure and may have cleared the virus and since seroreverted. It is also likely that a small proportion of people included in the database had false positive EIA/ELISA results at diagnosis and this may result in an overestimation of viral clearance.

Overall, 62% (n=784) of database participants had at least one positive RNA result in their charts and a further 15% (n=192) had positive hepatitis C confirmatory tests but no positive RNA results. The remaining 23% (n=299) tested ELISA/EIA positive/weak positive or RIBA/INNO-LIA indeterminate and had no other positive hepatitis C results (figure 10).

Twenty four percent (n=37) of participants infected through clotting factors had no RNA results in their charts. All were deceased and most had died in the early 1990s. These participants were found to be similar to participants who ever tested RNA positive in terms of liver-related outcomes. Therefore, it is likely that a large proportion had circulating virus.

The overall spontaneous viral clearance rate by the time of diagnosis was 36%. However, as stated above, some participants did not have positive confirmatory results for hepatitis C. A small proportion of these may have had false positive ELISA/EIA results, making the viral clearance rate appear higher than it was. When only participants with positive confirmatory results were analysed, 20% had cleared the virus spontaneously by the time they were diagnosed. Therefore, the true rate is likely to be somewhere between 20 and 36%.

Spontaneous viral clearance varied by sex. Females (n=408, 41%) were significantly more likely to have cleared the virus by the time of their diagnosis than males (n=36, 15%) (figure 9). This was true even when only participants who had positive confirmatory results for hepatitis C were considered (22% compared to 11%). A systematic review of 31 studies of acute hepatitis C found a mean spontaneous viral clearance rate of 26% and also found that viral clearance was significantly higher for females (42%) compared to males (20%).[23]

Much of the subsequent analysis is presented separately for participants who ever tested RNA positive and those who had RNA tests done but had no positive RNA results in their charts. As most participants were diagnosed some years after infection, ever testing RNA positive was found to be an excellent indicator of chronic long-term infection. Most of those who ever tested RNA positive and subsequently cleared the virus have done so relatively recently as the median duration of RNA positivity for those who ever tested positive (28 years) was found to be similar to the median time between infection and end of latest follow-up (29 years). We have no way of knowing the timing of viral clearance for participants who cleared the virus prior to testing (no positive RNA results). However, studies have found that spontaneous viral clearance usually occurs within two years of infection [23,24] The participants who had no RNA results in their charts were omitted from most of the analyses by RNA status as they could not be classified as either "ever" or "never" testing RNA positive and the aim of these analyses was to facilitate the comparison of participants who developed chronic infection and those who did not.

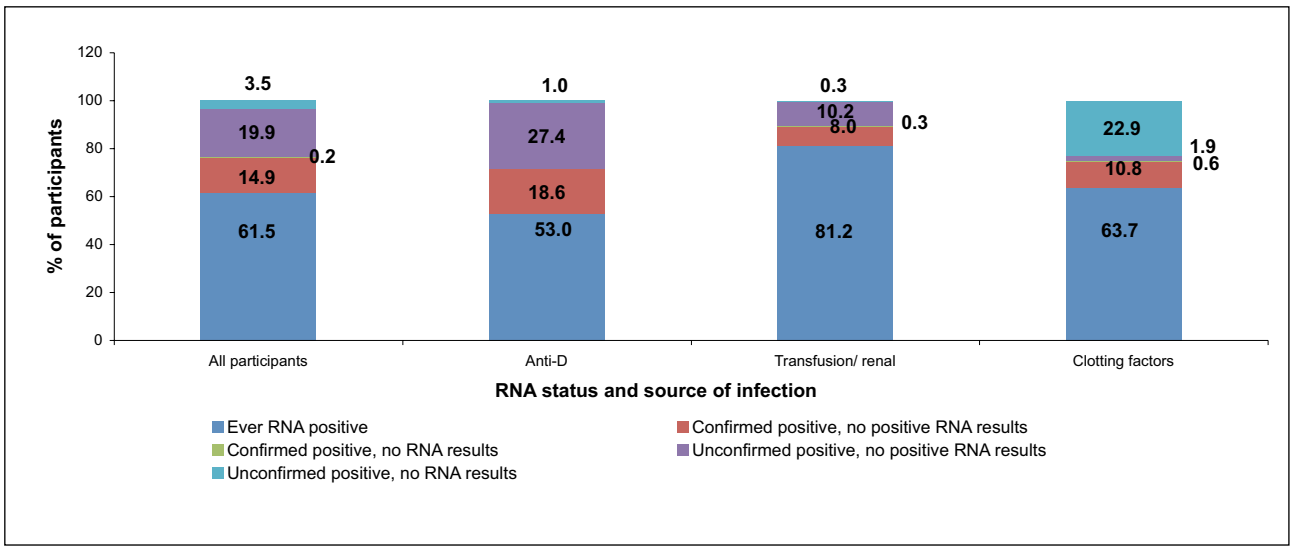

Figure 10. Hepatitis C RNA results for all participants and by source of infection (n=1275)

Genotype

The hepatitis C genotype was available for nearly all of the database participants who ever tested RNA positive (n=747, 95%). Genotype 1 predominated. Seventy six percent (n=568) were infected with genotype 1, 19% (n=139) were infected with genotype 3, 5% (n=36) were infected with genotype 2 and 0.5% (n=4) with genotypes 4 or 5 (figure 11).

The distribution of age at infection did not differ significantly by genotype, but that of sex and source of infection did. Genotype 1 was significantly more common in females compared to males and in anti-D participants compared to blood transfusion/renal or blood clotting factor participants. This is due to the large group of females infected with genotype 1 hepatitis C through batches of anti-D administered between 1977 and 1979. Ninety percent of participating anti-D participants, who have been genotyped, had genotype 1 hepatitis C compared to 59% of blood transfusion/renal participants and 65% of blood clotting factor participants (figure 11).

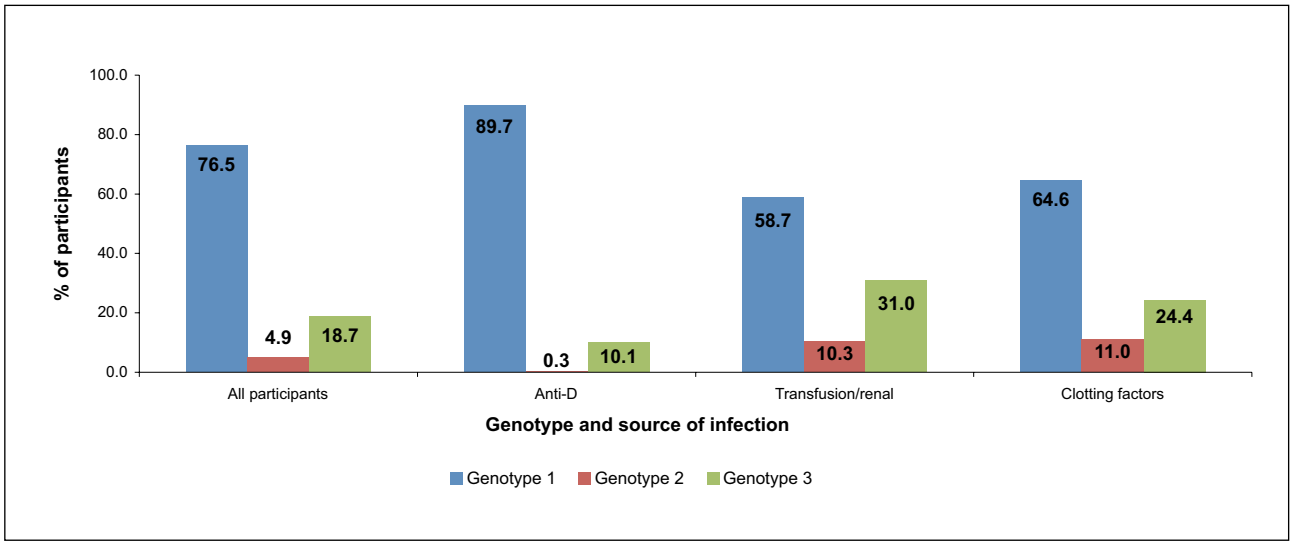

Figure 11. Distribution of hepatitis C genotypes by source of infection (n=740, genotypes 4 & 5 and source of infection=other omitted, n=7)

Alcohol consumption

If alcohol intake was recorded in participants' medical charts, it was entered into the database. The recommended upper limits for alcohol consumption in Ireland are 21 units per week for males and 14 units per week for females. Participants consuming between these limits and 40 units per week were classified as having moderately high alcohol intake and those consuming over 40 units were classified as having high alcohol intake. Alcoholic liver disease or alcohol abuse was also recorded in the charts of 66 participants. This additional information was combined with alcohol intake data when looking at the effects of alcohol on disease progression and these participants were considered to have had high alcohol intake.

Some data on units of alcohol were available for 89% of all participants and 91% of participants who ever tested RNA positive. Alcohol intake in excess of the recommended limits was recorded in the medical charts of 12% of database participants for whom data were available (table 9). Data completeness was much better at first visit to the hepatology units (n=1078, 85%). Alcohol consumption at last visit to the hepatology unit was recorded for 31% (n=389) of participants at the time of baseline or follow-up data collection. Where data at more recent visits were available, 6% (n=24) of participants consumed alcohol in excess of recommendations (table 10).

*Table 9. Highest recorded alcohol intake for all database participants and by RNA status (where data available, n=1132, 89%)**

Alcohol consumption	Ever RNA positive participants (%)	Never RNA positive participants (%)	All (%)*
Non drinker	181 (25.4)	104 (25.9)	289 (25.5)
Within recommended limits	436 (61.1)	268 (66.7)	711 (62.8)
Moderately high	39 (5.5)	15 (3.7)	55 (4.9)
High	58 (8.1)	15 (3.7)	77 (6.8)
Total	**714**	**402**	**1132**

** no alcohol intake data available for 143 database participants, RNA status not known for 16 participants with alcohol intake data*

*Table 10. Alcohol intake at most recent visit (recorded at baseline or follow-up data collection) for all participants and by RNA status (where data available, n=389, 31%)**

Alcohol consumption	Ever RNA positive participants (%)	Never RNA positive participants (%)	All (%)*
Non drinker	125 (44.0)	44 (44.9)	173 (44.5)
Within recommended limits	144 (50.7)	46 (46.9)	192 (49.4)
Moderately high	10 (3.5)	7 (7.1)	18 (4.6)
High	5 (1.8)	1 (1.0)	6 (1.5)
Total	**284**	**98**	**389**

** no recent alcohol intake data available for 886 database participants, RNA status not known for 7 participants with alcohol intake data*

Changes in alcohol consumption between first visit and baseline/follow-up data collection for participants who ever tested RNA positive

Data at first and more recent visits to the hepatology unit were recorded for 32% (n=284) of ever RNA positive participants. There was no change in alcohol consumption for 58%, 19% had decreased their consumption from within recommended limits to not drinking at all, 13% had decreased their consumption

from over the recommended limits to within limits or not drinking at all and 10% had increased their consumption from within recommended limits or not drinking to over the recommended limits.

Differences in alcohol consumption by sex and source of infection

Males and females differed in their reported exposure to alcohol with 33% of males exceeding the recommended limits for alcohol intake compared to 7% of females (figure 12). These proportions did not differ by RNA status. Alcohol consumption also differed by source of infection with participants infected through anti-D significantly less likely to consume alcohol in excess of recommendations compared to those infected through other means. However, this is likely to be largely attributable to the differences in sex distribution by source of infection (figure 13).

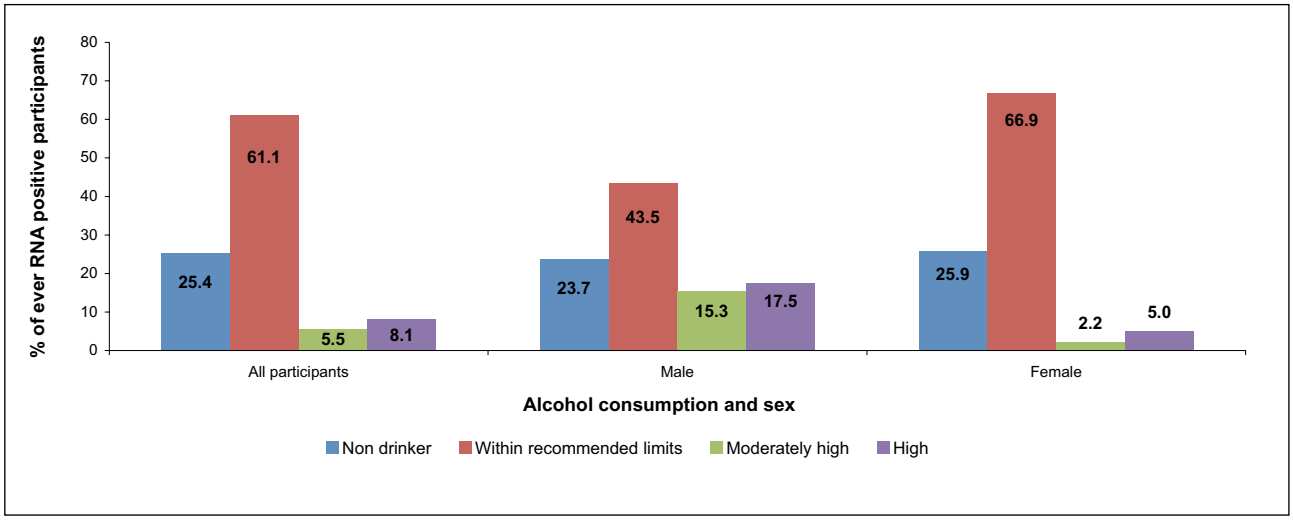

Figure 12. Distribution of highest reported alcohol consumption by sex for participants who ever tested RNA positive (where data available, n=714, 91%)

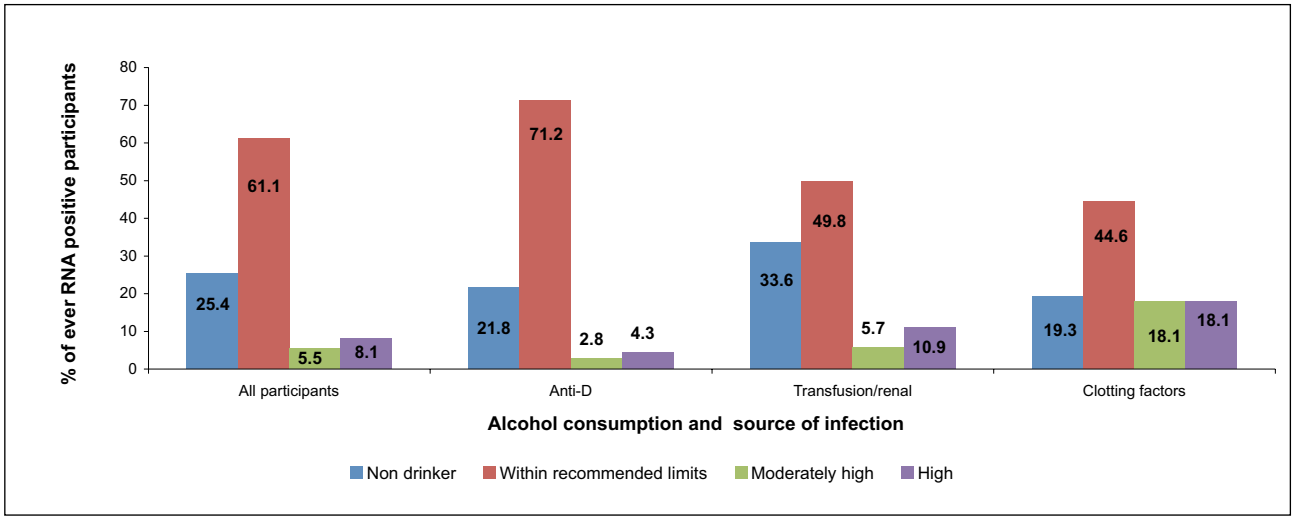

Figure 13. Distribution of highest reported alcohol consumption, by source of infection for participants who ever tested RNA positive (where data available, n=711, 91%)

Outcomes

Medical conditions

Almost all participants had medical conditions, other than hepatitis C and their index condition (e.g. haemophilia), recorded in their charts (table 11). These were not necessarily conditions that were diagnosed according to standardised criteria and may be unrelated to hepatitis C infection. Some medical conditions may also be underestimated if they are treated privately and not discussed with the consultant hepatologist. Without a comparison group, it is not possible to determine if the prevalence of these conditions and procedures differed from the general population. However, we would expect to see a significant difference in the prevalence of a condition between RNA positive and never RNA positive participants if it was strongly associated with hepatitis C infection.

Depression was recorded in the medical charts of 342 participants and anxiety was reported for a further 49. The prevalence of both was significantly higher for ever RNA positive participants compared to those who never tested RNA positive (table 11). Females were more likely to report depression than males and participants who had received anti-viral treatment were more likely to have depression recorded in their medical charts after accounting for the effects of sex and RNA status. Long-term medications for depression, sleep disorders or anxiety were noted in the charts of 54% of those with depression or anxiety.

Osteoporosis and osteopaenia were also more likely to be recorded for participants who ever tested RNA positive. Older age and female sex were also risk factors for both conditions.

Twenty five percent of ever RNA positive females had partial or full hysterectomies or other operations on the uterus compared to 19% of those who never tested RNA positive. However, the difference in prevalence by RNA status was not statistically significant after adjusting for age at latest follow-up. We are planning to investigate this further using data from the Hospital In-Patient Enquiry Scheme and a separate cross-sectional study.

The prevalence of diabetes was higher in participants who tested RNA positive, in males and those who were older at infection or older at latest follow-up. The prevalence of hypertension did not vary significantly by RNA status after accounting for the effects of older age.

*Table 11. Medical conditions recorded in charts of participants – most common conditions and other conditions of interest**

Medical condition	Number participants	% of participants	Number ever RNA positive	% of ever RNA positive participants	Number never RNA positive	% of never RNA positive participants
Fatigue & lethargy	392	30.7	257	32.8	131	29.5
Depression	342	26.8	248	31.6	91	20.5
Arthralgia/joint pain	308	24.2	190	24.2	117	26.4
Hypertension	229	18.0	162	20.7	67	15.1
Partial/full hysterectomy †	220	22.3	143	24.7	76	18.6
Osteoporosis/osteopaenia	167	13.1	125	15.9	42	9.5
Fibromyalgia	135	10.6	95	12.1	40	9.0
Appendicectomy	131	10.3	79	10.1	52	11.7
Cholecystectomy	131	10.3	90	11.5	41	9.2
Osteoarthritis	104	8.2	74	9.4	29	6.5
Dry or itchy eyes	87	6.8	62	7.9	25	5.6
Asthma	78	6.1	52	6.6	25	5.6
Hypothyroidism	76	6.0	52	6.6	24	5.4
Helicobacter pylori	74	5.8	51	6.5	23	5.2
Hypercholesterolaemia	64	5.0	29	3.7	35	7.9
Irritable bowel syndrome	64	5.0	39	5.0	25	5.6
Menorrhagia †	58	5.9	34	5.9	24	5.4
Hiatus hernia	56	4.4	36	4.6	20	5.9
Anaemia	51	4.0	33	4.2	18	4.1
Diabetes	80	6.3	62	7.9	17	3.8
Anxiety	49	3.8	39	5.0	10	2.3
Operations on joints or bones	48	3.8	39	5.0	9	2.0
Alcohol abuse	45	3.5	36	4.6	6	1.4
Pruritis	41	3.2	36	4.6	4	0.9
Arthritis/arthropathy	40	3.1	27	3.4	12	2.7
Eczema/dermatitis	38	3.0	26	3.3	12	2.7
Psoriasis	34	2.7	21	2.7	12	2.7
Grave's disease/ hyperthyroidism	34	2.7	24	3.1	10	2.3
Coeliac disease	28	2.2	13	1.7	14	3.2
Sicca/Sjorgen syndrome	25	2.0	18	2.3	7	1.6
Thyroidectomy	13	1.0	9	1.1	4	0.9
Parathyroidectomy	12	0.9	10	1.3	2	0.5
Cryoglobulinaemia	7	0.5	6	0.8	1	0.2
Parkinson's Disease	5	0.4	3	0.4	2	0.5
Non Hodgkins's lymphoma	4	0.3	4	0.5	0	0.0

** All conditions where n>45 are included. Data for some other conditions mentioned in literature or raised by patient groups are also included.*
† Percentage calculated using female denominator figures.

Liver function tests – alanine aminotransferase (ALT)

Ninety five percent of participants had at least one ALT result in their charts. Levels were elevated for 55% of ever RNA positive participants and 10% of those with no positive RNA results. Abnormally high ALT results were also significantly more common in males, participants with cirrhosis and those infected for longer durations.

Signs of liver disease

One hundred and forty eight (11.6%) participants had one or more signs of liver disease recorded in their charts at latest follow-up (table 12). Ninety three percent of these (n=137) tested RNA positive at some stage, 4% (n=6) had no RNA results in their charts and 3% (n=5) never tested RNA positive. The most common conditions recorded were cirrhosis, ascites, varices, portal hypertension and hepatomegaly.

Table 12. Number and percentage of participants with signs of liver disease by RNA status

Signs of liver disease	Number ever RNA positive participants (%)	Number never RNA positive participants (%)	All (%)*
Cirrhosis	93 (11.9)	0	97 (7.6)
Varices	43 (5.5)	0	45 (3.5)
Ascites	37 (4.7)	3 (0.7)	41 (3.2)
Portal hypertension	37 (4.7)	0	38 (3.0)
Hepatomegaly	36 (4.6)	3 (0.7)	39 (3.1)
Splenomegaly	34 (4.3)	1 (0.2)	35 (2.7)
Liver tumour/HCC	20 (2.6)	0	22 (1.7)
Encephalopathy	17 (2.2)	1 (0.2)	19 (1.5)
Hepatic decompensation	9 (1.2)	0	10 (0.8)
One or more signs of liver disease	**137 (17.5)**	**5 (1.1)**	**148 (11.6)**

**6 participants with one or more signs of liver disease (including 4 with cirrhosis and 2 with liver tumours) had no RNA results in their charts*

Cirrhosis

By latest follow-up, 12% (n=93) of ever RNA positive participants had developed cirrhosis (table 12, figure 14). Fifty seven were female (10% of RNA positive females) and thirty six were male (18% of RNA positive males). Four deceased participants with no RNA results in their charts had also developed cirrhosis.

The number of participants with cirrhosis has increased by 23 since baseline data collection. Nine were new database participants and seven were participants who had cirrhosis at baseline but this was originally recorded on their death certificate or in the comments field rather than as test results. These data were not analysed at baseline when looking at cirrhosis. The remaining seven participants were newly diagnosed with cirrhosis since baseline data collection was done.

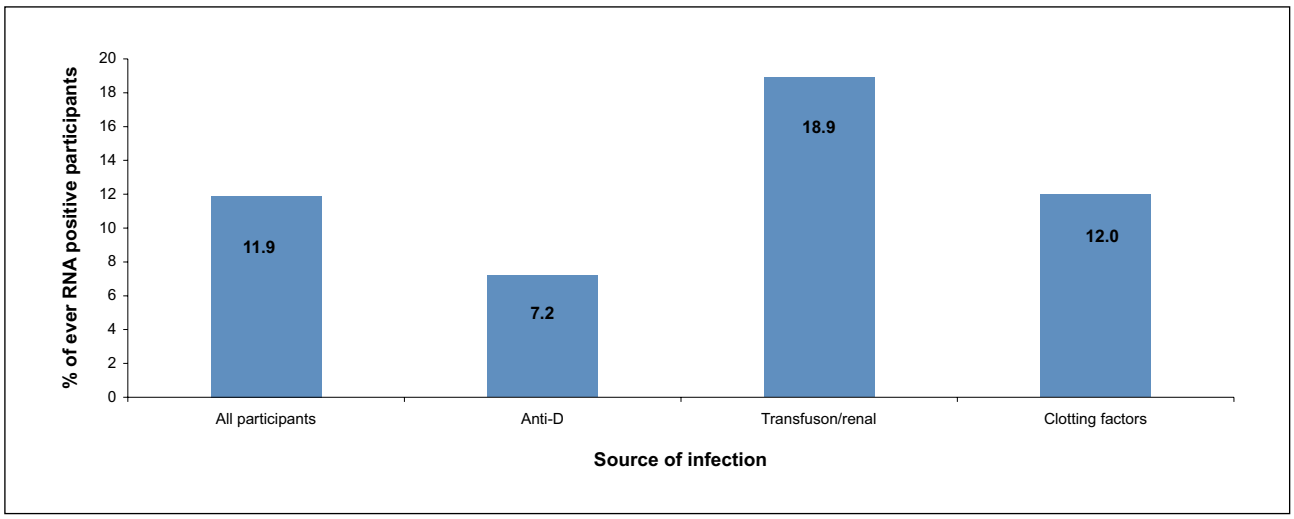

Figure 14. Percentage of ever RNA positive participants with cirrhosis by end of latest follow-up, by source of infection

The median duration of infection at the estimated date of cirrhosis (see chapter 3) was 20.5 years and the median age at cirrhosis was 51 years. This time to development of cirrhosis was similar to the mean value of 20.6 years found by Tong et al,[25] even though their cohort was slightly older and their study was set in a tertiary referral centre which meant that participants with more severe disease were likely to be over-represented. However, participants with known alcoholic liver disease were excluded from their study.

After RNA status, alcohol consumption was the biggest determinant of risk of cirrhosis in the database cohort. Where alcohol data were recorded, 27% of participants with cirrhosis had high alcohol consumption compared to 5% of those without. Males were significantly more likely than females to develop cirrhosis after taking account of reported alcohol consumption, age at infection, duration of infection and RNA status. Participants with genotype 3 hepatitis C, those aged 60 years or older at end of latest follow-up, those infected for 20 years or more, those infected when aged 35 or older and those infected through blood transfusions were also at higher risk of developing cirrhosis.

An exclusively female German anti-D cohort infected with genotype 1b hepatitis C and followed for 25 years was very similar to the Irish anti-D cohort infected between 1977 and 1979.[26] Disease progression appears to have been slower in the German cohort but the median duration of follow-up was slightly shorter. Two percent (n=11) of viraemic participants had incomplete or complete cirrhosis in the German cohort, whereas seven percent of the ever RNA positive Irish anti-D participants had cirrhosis at latest follow-up.

In contrast, a UK cohort infected through contaminated blood transfusions appears to have experienced faster disease progression.[6] After approximately ten years of infection, 9.7% had developed cirrhosis compared to 12% of Irish RNA positive database participants who had a median duration of infection of 29 years. However, the UK participants were older at infection (median age 43.6 years) and older age at infection has been found to be an important determinant of disease progression.[3]

Hepatocellular carcinoma (HCC)/liver cancer

By latest follow-up, 20 (3%) ever RNA positive participants and two participants with no RNA results had developed HCC or liver cancer (table 4). Eight were female (1.4% of RNA positive females) and twelve were male (5.8% of RNA positive males). Thirteen were infected through blood transfusions, six were infected through blood clotting factors and three were infected through anti-D.

This is an additional 12 participants compared to baseline. Six were new to the database, two were participants who had liver cancer at baseline but this was originally recorded on their death certificate or in the comments field rather than as test results. These data were not analysed at baseline when looking at liver tumours. The remaining four participants were newly diagnosed with liver cancer since baseline data collection was done.

Sixteen of the participants with HCC were known to be deceased. The cause of death was directly liver-related for fourteen, not liver-related for one and the death certificate was missing for the remaining participant. The median duration of infection at the estimated date of HCC was 22 years and the median age at HCC was 66 years.

Biopsy results

Seven hundred and sixty three database participants had one or more biopsies. This varied by RNA status with 83% of those ever testing positive having a biopsy compared to 25% of those with no positive RNA results. Participants infected through contaminated clotting factors were least likely to have had biopsies, with only 34% of those ever testing RNA positive having biopsy results in their charts compared to 96% of ever RNA positive anti-D participants and 80% of those infected through blood transfusions or treatment for renal disease. Disease progression may be more likely to be monitored using ultrasounds, CT scans and other tests for participants infected through clotting factors and the distribution of fibrosis scores may be unreliable for this group because of small numbers.

Biopsy results included inflammation grade and fibrosis stage. The degree of liver inflammation can fluctuate over time and can be affected by recent alcohol intake, obesity, diabetes and prescription or non-prescription drugs. Fibrosis scores provide a better indication of disease progression.

Inflammation

Twenty five percent (n=158) of ever RNA positive participants had moderate or severe inflammation on last biopsy (figure 15). This varied by source of infection with 33% (n=68) of ever RNA positive blood transfusion/renal participants having moderate or severe inflammation on last biopsy compared to 21% (n=83) of anti-D participants and 21% (n=7) of clotting factor participants.

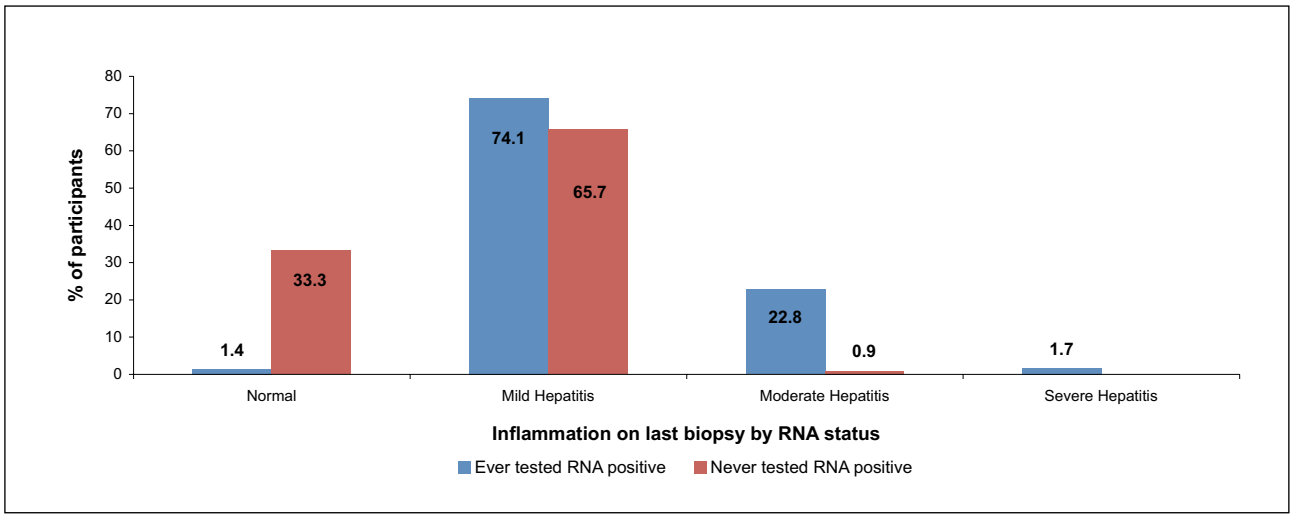

Figure 15. Inflammation grade on last biopsy by RNA status (n=755)

Fibrosis

Fibrosis was scored using different scoring systems in different units. The most recent biopsy was scored using a 0-6 scoring system for 76% (n=558) of participants and a 0-4 scoring system for the remaining 24% (n=178). Last available fibrosis scores for all participants are shown in figures 16 and 17.

We considered high fibrosis scores to be scores of 4-6 on biopsies scored from 0-6 and scores of 3-4 on biopsies scored from 0-4. Seventeen percent (n=109) of ever RNA positive participants had a high fibrosis score on most recent biopsy compared to 4% (n=4) of those who never tested RNA positive. Fibrosis also varied by source of infection. Thirty percent (n=59) of ever RNA positive blood transfusion/renal participants had a high fibrosis score on most recent biopsy compared to 24% (n=8) of clotting factor participants and 11% (n=42) of anti-D participants (figure 18).

Factors associated with ever having high fibrosis scores include ever testing RNA positive, older age at infection, male sex, high alcohol intake and having genotype 3 infection. Participants infected through blood transfusions/treatment for renal disease were significantly more likely to have high fibrosis scores compared to those with other sources of infection after accounting for the effects of RNA status, age at infection, duration of infection and alcohol consumption.

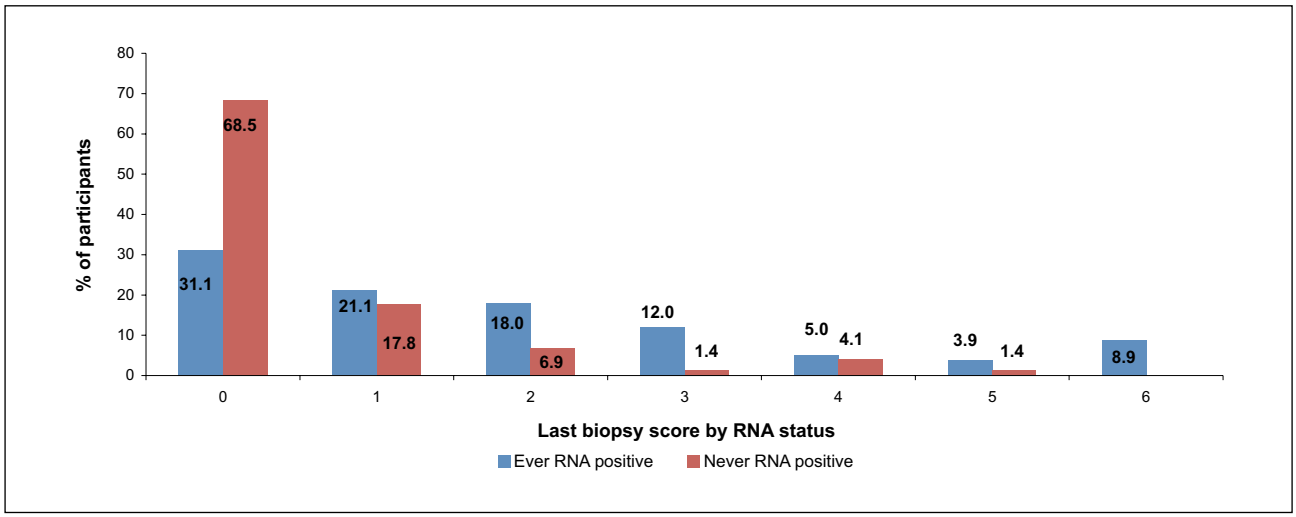

Figure 16. Fibrosis score on last biopsy for biopsies scored from 0 to 6 (n=558), by RNA status

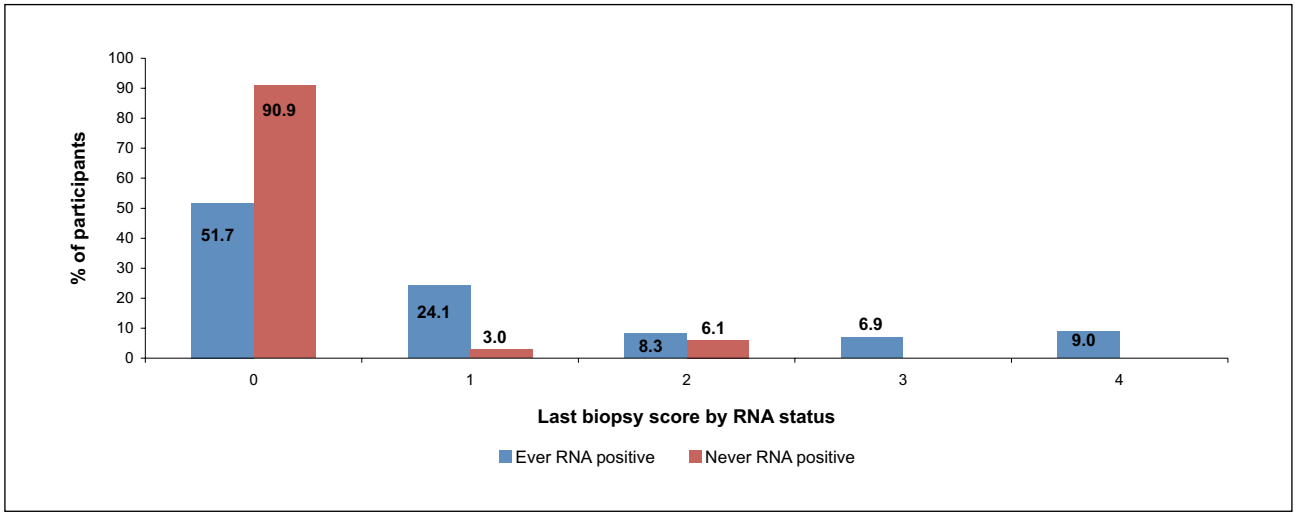

Figure 17. Fibrosis score on last biopsy for biopsies scored from 0 to 4 (n=178), by RNA status

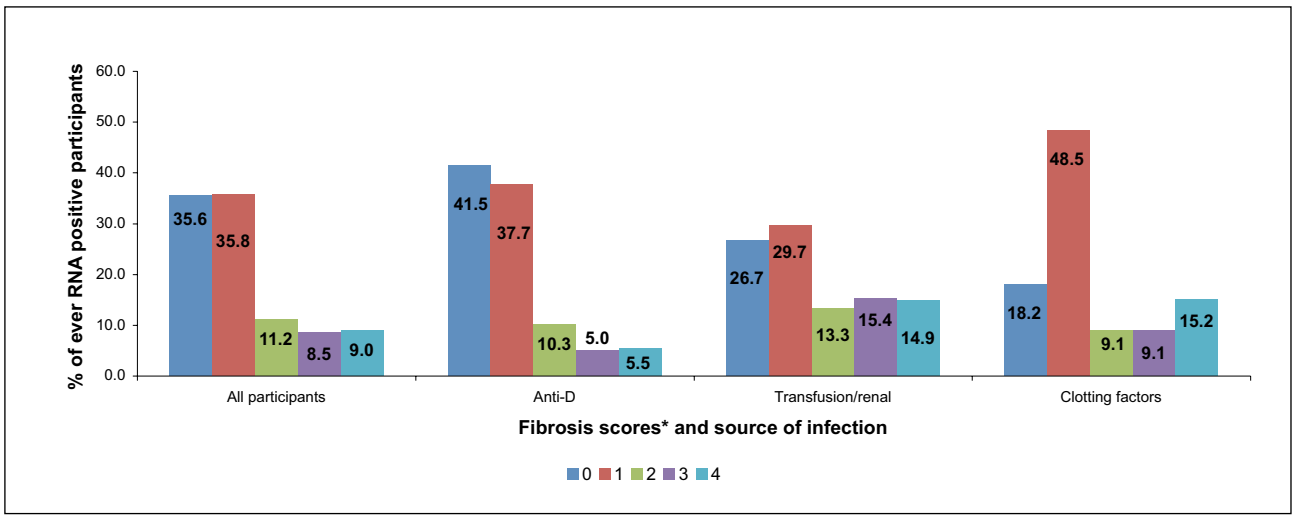

Figure 18. Fibrosis on last biopsy for ever RNA positive participants by source of infection (n=626)*
**All 0-6 scores standardized to 0-4 (see chapter 3 for description) to allow all biopsies to be analysed together.*
Results for clotting factor participants may not be representative as data only available for 33 and last biopsy was many years ago for a large proportion

Rate of fibrosis for untreated ever RNA positive participants

Five hundred and ninety three RNA positive participants had biopsy results with fibrosis scores without undergoing anti-viral treatment or transplants. The median duration of infection at last scored biopsy for these participants was 20 years and eighteen percent had high fibrosis scores (3/4 if biopsy scored from 0 to 4 and 4/5/6 if biopsy scored from 0 to 6). Biopsies scored from 0 to 6 were converted to the 0 to 4 scores (see chapter 3 for details) to assess the median rate of fibrosis progression for these participants. The overall estimated fibrosis rate was 0.043 units per year of infection (range: 0-1.022). Estimated annual fibrosis rates were higher for males (0.076), participants infected when aged over 40 years (0.187), participants with genotype 3 hepatitis C (0.145) and those with high alcohol consumption (0.148). Estimated fibrosis rates were very low for females who were infected when aged 40 years or younger and who did not have high levels of alcohol consumption (0.039).

Poynard et al[3] carried out a large scale study looking at fibrosis progression. They estimated the time from infection to cirrhosis to be 20 years in those aged over 40 years at infection (Irish database estimate: 21 years), 24 years in those with high alcohol consumption (Irish database estimate: 27 years), 24 years in those with genotype 3 hepatitis C (Irish database estimate: 28 years) and 42 years in females who did not have high alcohol intake and were infected at less than 40 years of age (Irish database estimate: >50 years).

Changes in biopsy results post treatment

One hundred and six RNA positive participants had pre- and post-treatment biopsy results. All were scored using the same scoring system at both biopsies. The change in fibrosis scores (all standardised to 0 to 4 system) by treatment response are shown in figure 19. Fibrosis scores worsened for 24% (n=16) of those who did not achieve sustained virological response (SVR) on treatment compared to 5% (n=2) of those who did. A significant proportion of those who were treated but did not achieve SVR showed improvements in biopsy scores post treatment (n=21, 31%).

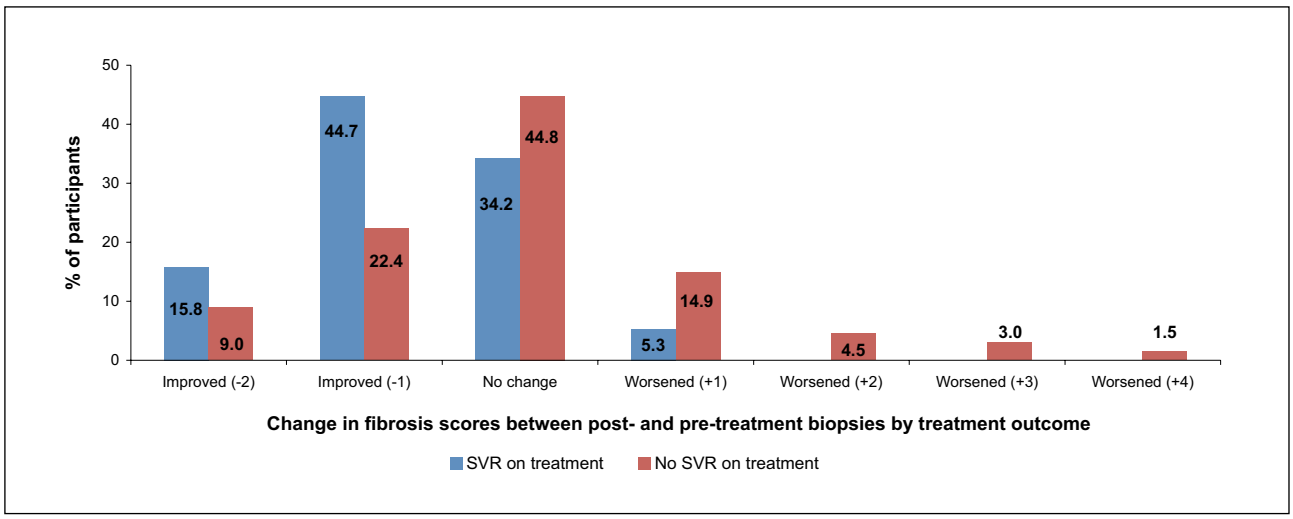

Figure 19. Changes in fibrosis scores (0-4) after treatment, by SVR status for participants who had pre- and post-treatment biopsy results (n=106)

**All 0-6 scores standardized to 0-4 (see chapter 3 for description) to allow all biopsies to be analysed together. Numbers in some categories are very low and percentages should be interpreted with caution.*

Deceased participants

One hundred and seventy three participants had died by latest follow-up. This represents 63 additional deceased participants compared to baseline. Fifty two were new participants, fifty of whom were infected through contaminated blood clotting factors and were identified in collaboration with the NCHCD. The remaining eleven deceased participants had consented at baseline and died since then.

Where death certificates were available (n=165), death was directly caused by liver disease for 43 participants (table 13). Thirty three had tested RNA positive, eight had no RNA results in their charts and the remaining two had RNA results in their charts, but had never tested RNA positive. Hepatitis C was one of the causes of death listed on the death certificate for thirty four. The underlying cause of death was coded to hepatitis C for nineteen, liver cell carcinoma for twelve, hepatic failure for three, cirrhosis of the liver for three and other liver related conditions for six. Data on alcohol consumption were available for 34 of the participants who died from liver disease and 53% (n=18) had high alcohol consumption.

The most common non-liver related causes of death were cancer, heart disease, renal disease and HIV/ immunodeficiency (discussed in more detail in the section 'Hepatitis C and HIV co-infected participants').

Table 13. Number and percentage of participants who died directly from liver-related disease, by source of infection

Source of infection	Died directly from liver-related disease*	% of participants who died from liver-related disease	% of ever RNA positive participants who died from liver-related disease
Anti-D	7	0.9	1.2
Transfusion/renal	18	5.5	6.4
Clotting factors	17	10.8	10.0
Total	**42**	**3.3**	**4.1**

**1 additional patient who died from liver-related disease missing information relating to source of infection*

All-cause mortality rates were significantly higher in participants who had ever tested RNA positive (figure 20) and those with no RNA results in their charts (most of whom had died) compared to those who had no positive RNA result at diagnosis. Mortality rates were also higher in participants with high alcohol consumption, males, participants co-infected with HIV and hepatitis C and those who were older at infection

or at latest follow-up. Mortality rates varied by source of infection with participants who were infected through blood transfusions/treatment for renal disease or blood clotting factors having higher mortality rates than those infected through anti-D.

Harris et al [27] found no difference in all-cause mortality between people who had been infected with hepatitis C and a control group after 16 years of infection. However, the age and sex distributions of the Irish and UK cohorts were quite different.

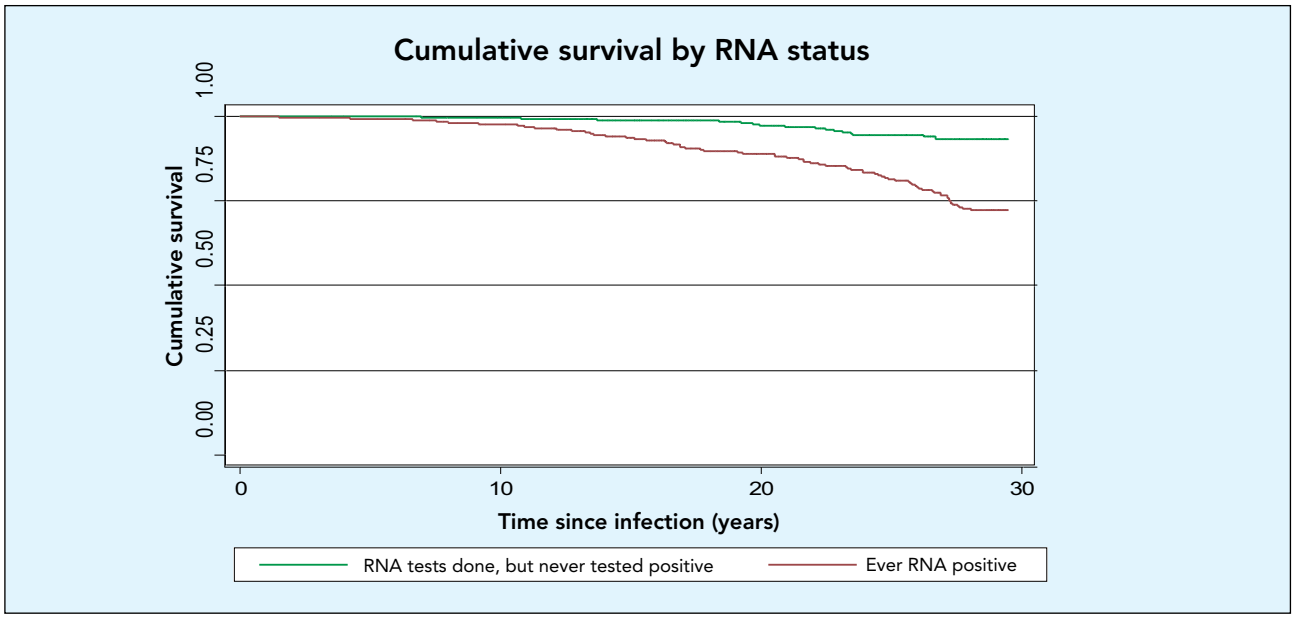

Figure 20. Comparison of survival for participants who ever tested hepatitis C RNA positive and those with RNA results in their chart but with no positive results

Liver-related mortality rates were also higher in participants who remained chronically infected or had no RNA results compared to those who had no positive RNA results in their charts (table 13). High alcohol intake was the most significant predictor of liver-related mortality.

Anti-viral treatment

Almost 40% (n=309) of ever RNA positive participants had one or more courses of anti-viral treatment by latest follow-up (table 14). Participants with higher fibrosis scores, with genotype 2 or 3 and those infected through clotting factors were more likely to have been treated (figure 21). Treated participants were also younger and infected for shorter durations compared to those who have not yet been treated.

Table 14. Number and percentage of RNA positive participants treated by number of treatment courses

Number of treatment courses	Number of participants	% of RNA positive participants
1	229	29.2
2	61	7.8
3 or more	19	2.4
Ever treated	**309**	**39.4**

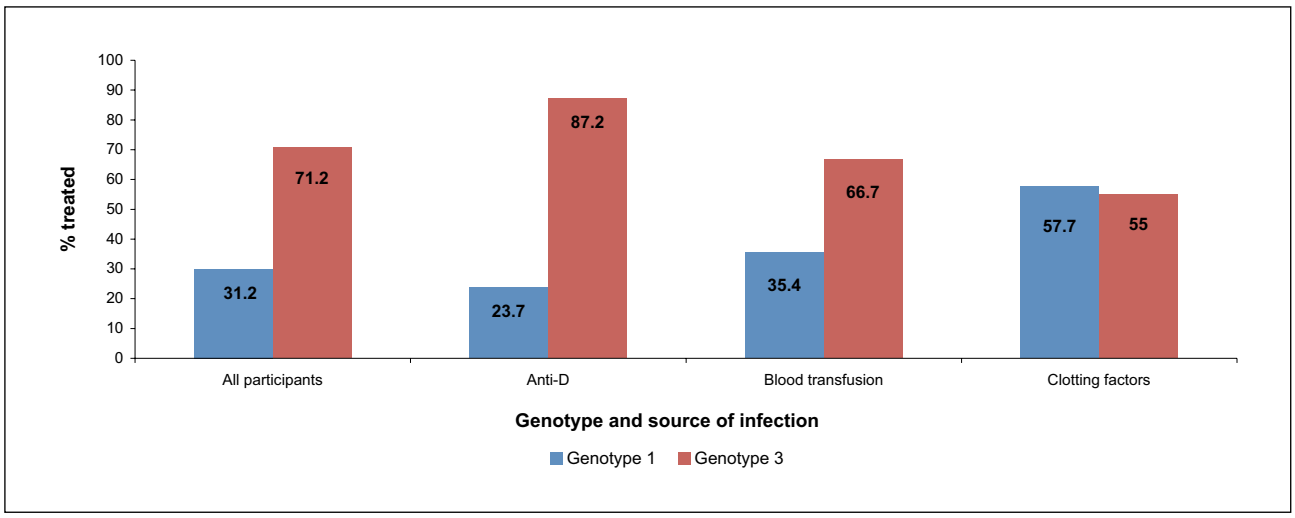

Figure 21. Percentage of participants treated, by genotype and source of infection (data for genotype 2 not shown as these were unreliable due to small numbers)

The SVR rate has improved in recent years with the advent of combined therapy with pegylated interferon and ribavirin (figure 22). The SVR rates shown for 2006 and 2007 are not reliable due to the small numbers of participants completing treatment. Tolerance of anti-viral treatment remains an issue, with 25% of all treatment courses stopped early due to side effects. All analyses of treatment outcomes were done on an intention-to-treat basis and participants stopping treatment early are included when calculating SVRs.

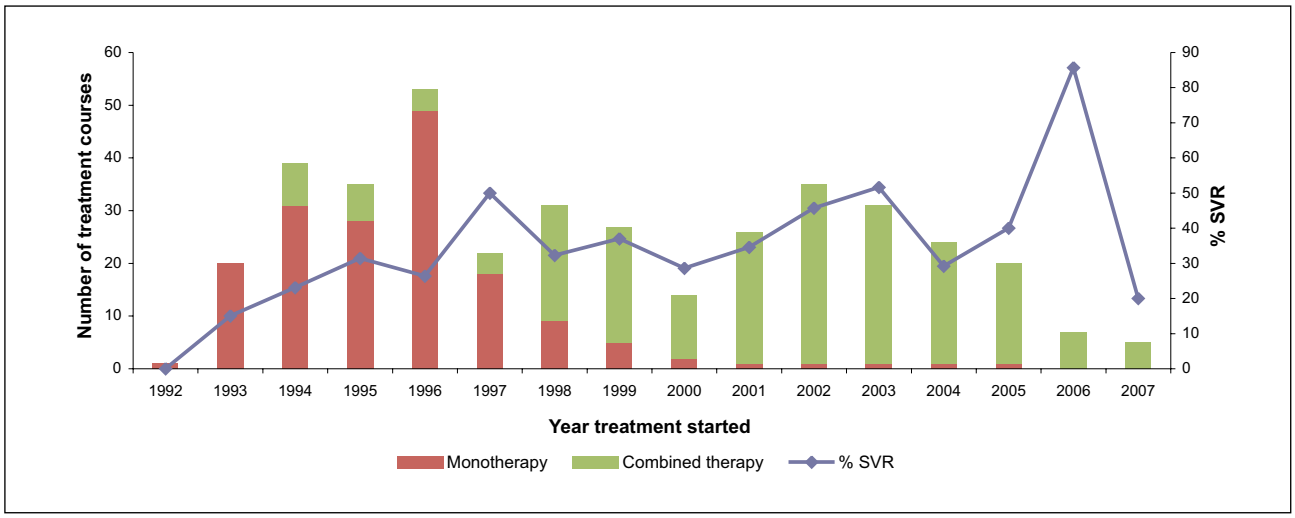

Figure 22. Treatment courses by type of treatment and percentage sustained virological response, 1992-2007 (outcome awaited for 18 participants – not included when calculating SVR)

The factors associated with SVR on first treatment were: treatment with combined therapy rather than monotherapy, longer duration of treatment (48+ weeks better than 24-47 weeks, better than <24 weeks), having hepatitis C genotype 3 rather than genotype 1, younger age at treatment and shorter duration of infection at treatment. Participants whose ALT levels were elevated on last test were also less likely to have a SVR. Neither source of infection nor sex affected treatment response after accounting for the effects of genotype, treatment regime, duration of infection and age (table 15, figure 23, figure 24).

Table 15. Number and percentage of ever RNA positive participants treated, and percentage SVR, by hepatitis C genotype, sex, source of infection and age at treatment

Characteristic		Number treated	% treated	% SVR on first treatment	% SVR any treatment
All participants		**309**	**39.4**	**34.8**	**46.1**
Genotype	1	177	31.2	19.9	29.0
	2	24	66.7	41.7	66.7
	3	99	71.2	55.7	67.7
Sex	Males	99	48.1	33.3	46.9
	Females	210	36.3	35.5	45.6
Source of infection	Anti-D	130	31.2	33.6	43.6
	Transfusion/renal	129	48.9	36.8	46.4
	Clotting factors	50	50	32.7	51.0
Age at treatment	0-44	156		42.3	
	45+	140		26.4	

Genotype not available for 8 participants who were treated and participants with genotypes 4/5 omitted from analysis of treatment data. Treatment outcome awaited for 18 participants – these participants were not included when calculating SVR.

Treatment response: naïve participants

The most important determinants of response to anti-viral treatment were hepatitis C genotype, type of treatment regime and duration of treatment. The overall SVR rate for treatment naïve genotype 3 participants was 56% compared to 20% for genotype 1 participants (table 15, figure 23).

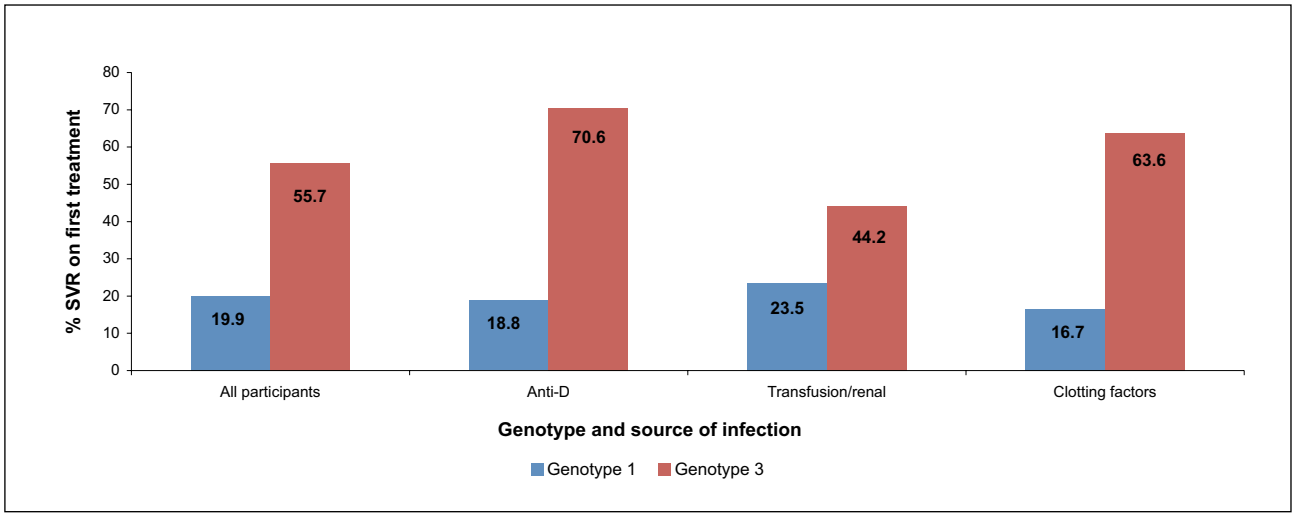

Figure 23. Percentage sustained virological response for treatment naïve participants by genotype and source of infection (data for genotype 2 not shown due to small numbers)

The current recommended treatment for hepatitis C is combined therapy with pegylated-interferon and ribavirin. Significant improvements in response rates have been achieved for both genotype 1 and genotype 3 infections when using combined therapy compared to monotherapy. Treatment response data by genotype and type and duration of treatment are shown in figure 24.

Eighty nine percent (n=8) of genotype 3 participants on combination therapy for 48 weeks or more achieved an SVR compared to 46% (n=18) of genotype 1 participants on the same treatment. The response rate in these genotype 3 participants is very high butt these results should be interpreted with caution as the number of genotype 3 participants in each treatment category was low. Large-scale clinical trials have reported SVR rates of 76-82% in genotype 3 patients and 42-46% in genotype 1 patients on this treatment regime.[14]

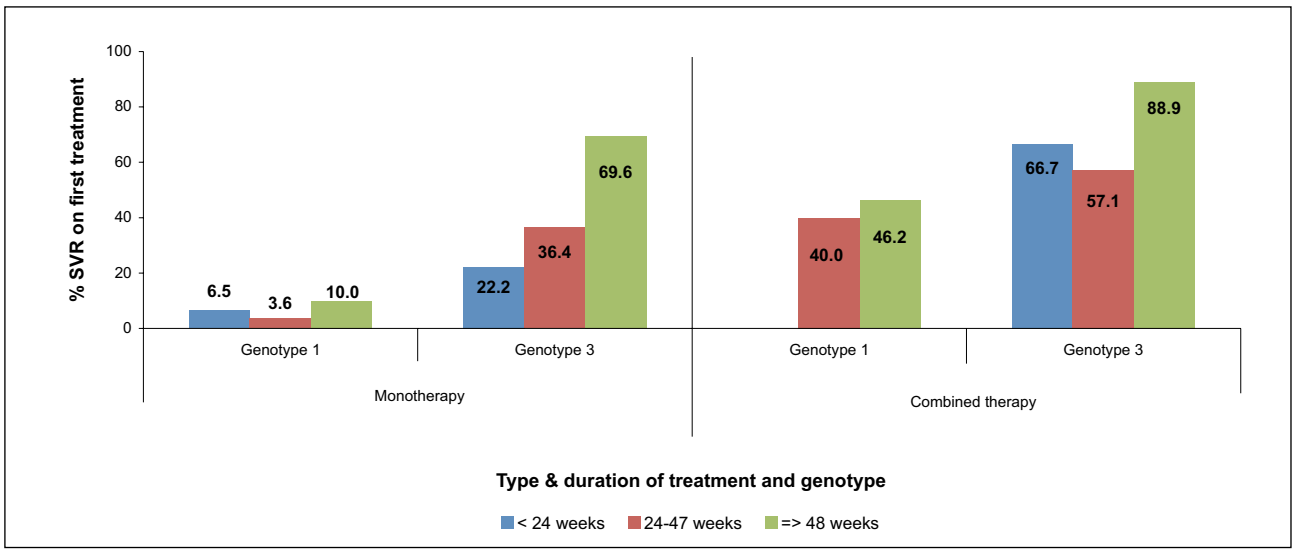

Figure 24. Percentage sustained virological response for treatment naïve participants by genotype and duration of therapy for monotherapy with IFN (n=148) or Peg-IFN (n=1), and combined therapy with IFN and RBN (n=81) or Peg-IFN and RBN (n=79). Data for genotype 2 not shown due to small numbers

Treatment response: previously treated participants

Eighty participants had at least two courses of treatment by end of latest follow-up. Six were still on treatment when follow-up data were collected. Of the remaining participants, the second treatment was with monotherapy for 17 and with combination therapy for 57. The numbers involved were small but there was some success when participants were re-treated using combination therapy, with 22% of those with genotype 1 and 50% of those with genotype 3 achieving SVR.

Hepatitis C and HIV co-infected participants

Sixty eight (43%) of the participants infected as a result of contaminated clotting factors were also infected with human immunodeficiency virus (HIV).

RNA results were available for 53% (n=37) and all except one were positive for circulating virus. The only positive hepatitis C results for thirty were from EIA/ELISA tests. Although these participants were classified as unconfirmed positives in the database project, this was due to lack of data rather than indeterminate or negative results and these participants looked similar to the ever RNA positive participants in terms of liver-related outcomes. By latest follow-up, 21 co-infected participants (31%) had one or more signs of liver disease, including 7 with cirrhosis (10.3%). Co-infected clotting factor participants had higher odds of having one or more signs of liver disease compared to clotting factor participants infected with hepatitis C alone. However this finding should be interpreted with caution as the numbers involved were low.

The database is unlikely to be an effective tool in looking at the natural history of disease progression in co-infected participants as sixty two percent (n=42) are now deceased. Most died in the early to mid 1990s. The median age at death was 35.5 years. Death certificates were not available for three. The underlying cause of death on the death certificate was HIV infection for twelve and a further ten had causes of death relating to immunodeficiency, but the term HIV was not specifically mentioned on their death certificate. Anecdotally, this may have been related to the stigma associated with HIV infection at the time and the wish to maintain the confidentiality and dignity of the family. Of the remaining co-infected participants, eight died directly from liver-related causes.

Eighteen co-infected clotting factor participants had received anti-hepatitis C treatment at latest follow-up. Half achieved SVR. The number treated was too low to reliably assess if treatment response varied

with HIV status. However, the response rates did not look different from those who were not co-infected, with 75% of genotype 3 and 30% of genotype 1 co-infected participants responding to treatment.

We are aware that a total of 105 people were co-infected with hepatitis C and HIV in Ireland as a result of contaminated clotting factors. Sixty seven have died (communication from Irish Haemophilia Society).

Liver transplants

Ten people had received liver transplants when the baseline data were collected. There were five additional transplanted participants at the end of the first year of follow-up. Three of these were newly transplanted people and two were new database participants who had been transplanted some years previously. The median age at transplant was 51 years and the median duration of hepatitis C infection at transplant was 27 years. All transplant recipients were RNA positive when transplanted and all of those tested post-transplant (n=13) remained RNA positive.

A further five database participants were on the waiting list for a liver transplant at the end of the first year of follow-up. Four had cirrhosis. Three deceased participants had been on the transplant waiting list.

Summary of determinants of disease progression

As there were several outcome measures that could be used to indicate hepatitis C disease severity, a variable was created to summarise disease progression.

A participant was considered to have 'more severe disease' if they had:

- Died from liver-related disease **or**
- Had ever had one or more of the following signs of liver disease: cirrhosis, primary liver cancer, ascites, varices, decompensated liver disease, portal hypertension, encephalopathy, hepatomegaly or splenomegaly **or**
- Had ever had a fibrosis score of 3 or 4 on a biopsy scored from 0 to 4 or a score between 4 and 6 on a biopsy scored from 0 to 6

All other participants were classified as having 'less severe disease'. Using these criteria, 25% (n=196) of ever RNA positive participants, 21% (n=10) of participants with no RNA results and 2% (n=7) of those who never tested RNA positive were classified as having 'more severe' disease by latest follow-up.

The effects of some key host and virus characteristics on the odds of having 'more severe' disease were examined using multivariate logistic regression and the results of this are shown in table 16. Only participants who tested RNA positive at some stage were included in this analysis as 92% of the 213 participants with more severe disease had tested RNA positive and this approach allowed the effects of genotype to be assessed. In addition, participants with missing values for one or more of the variables in the model could not be included. Ultimately the logistic regression analysis was based on data from 160 participants with 'more severe' disease and 510 participants with 'less severe' disease.

Explanatory note:
The odds ratios shown are a measure of the odds of 'more severe' disease in one group (e.g males) divided by the odds of 'more severe' disease in another group (the reference group e.g. females). An odds ratio of 1 indicates that 'more severe' disease is equally likely in both males and females and an odds ratio of more than 1 for males indicates that 'more severe' disease is more likely in males.

Table 16. Factors associated with 'more severe' disease in participants who ever tested RNA positive – logistic regression model (n=670)

Factors associated with having more severe disease	Odds Ratio	P-value	95% Confidence interval
Alcohol consumption			
Non drinker/within recommended limits/moderately high	1	Reference	Reference
High (>40 units per week or alcohol abuse in chart)	5.19	<0.001	2.70-9.96
Age at infection			
0-34 years	1	Reference	Reference
35+ years	2.09	0.002	1.32-3.33
Alanine aminotransferase levels			
Normal ALT levels	1	Reference	Reference
Elevated ALT levels	1.63	0.02	1.08-2.45
Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	1.28	0.627	0.47-3.48
Genotype 3	1.90	0.023	1.09-3.29
Duration of RNA positivity & sex			
Females infected <20 years	1	Reference	Reference
Females infected 20+ years	3.49	0.001	1.62-7.51
Males infected <20 years	5.72	<0.001	2.39-13.73
Males infected 20+ years	5.84	<0.001	2.56-13.35

The determinants of having 'more severe' hepatitis C disease in the database cohort were high alcohol intake, male sex, older age at infection, longer duration of RNA positivity, elevated ALT levels and hepatitis C genotype 3. All associations between these characteristics and 'more severe' disease were statistically significant.

The most important determinant of disease progression was alcohol intake. Participants with high alcohol intake had five times higher odds of having 'more severe' disease than those without. Those infected when aged 35 years or older had twice the odds of 'more severe' disease than those infected when aged less than 35 years.

The influence of each of these factors on disease severity was independent of the effects of all of the other factors in the table except for duration of RNA positivity, which had different effects in males and females in this cohort. Females infected for twenty years or longer had 3.5 fold higher odds of 'more severe' disease compared to those infected for less than 20 years. Males infected for less than 20 years had more than 5-fold higher odds of 'more severe' disease compared to females infected for less than 20 years. Longer duration of infection did not further increase the odds of 'more severe' disease in males. However, the number of males infected for less than 20 years and included in this model was low (n=59), so this result may not be reliable (wide 95% confidence intervals). In addition, some of the co-infected clotting factor participants who have died had indicators of 'more severe' liver disease and would have died with shorter durations of infection. This is likely to have distorted the effects of duration of infection on disease progression in males.

This model also indicated that participants with genotype 3 had 1.9 fold higher odds of having 'more severe' disease compared to those with genotype 1. Most studies have found that while hepatitis C genotype is an important determinant of response to treatment, it does not impact on disease progression. There is a possible mechanism for genotype 3 to influence disease progression as there is a

biological association between genotype 3 and steatosis independently of BMI, and steatosis has been found to be associated with fibrosis progression.[28] However, it is also possible that this finding could be explained by the potential confounding effects of another factor not included in the model. For instance, we could not examine the effects of BMI on disease progression in the database cohort as BMI data were available for only a minority of participants. In addition, it is likely that the distribution of co-morbidities varied by source of infection and hence by genotype and this has not been accounted for.

To try and address this, we used logistic regression to model disease severity using the blood transfusion/ renal group alone. This was the only patient group where there were good proportions of both sexes and a wide distribution of ages. We would also expect co-morbidities to vary less within this group compared to within the entire database cohort. Only 213 people were included in the model, so results should be interpreted with caution. Longer duration of infection, male sex, older age at infection and high alcohol intake were associated with 'more severe' disease. Genotype 3 was also associated with 'more severe' disease after adjusting for all of the other variables (OR=2.7, p=0.004).

The effects of HIV infection were also examined. Co-infected participants had higher odds of 'more severe' disease, but co-infection was not found to be a statistically significant factor in disease progression. This is probably because the number of co-infected participants in the database was too low to detect a statistically significant effect (n=68).

Clinical management

Visits to the hepatology units

The frequency of attendance at the hepatology units is likely to vary depending on the clinical status of the participant and practices within the individual units. As would be expected, chronically infected participants were more likely to have attended their unit recently. Eighty three percent (n=557) of living, ever RNA positive participants had visited their hepatology unit within two years of the end of 2007 compared to 61% (n=259) of never RNA positive participants. Eighty six percent of the deceased participants who ever tested RNA positive and sixty three percent of those who had never tested RNA positive had attended their hepatology unit within two years of their death. The median number of outpatient appointments between baseline and follow up was three for ever RNA positive participants and two for never RNA positive participants.

Specialist health services and procedures

We looked at the use of specialist health services, other than hepatology, and medical procedures between baseline and follow-up data collection for participants with follow-up forms, and in the twelve months prior to data collection for new database participants. Fifty four percent (n=318) of ever RNA positive and forty one percent (n=112) of never RNA positive participants had attended one or more specialist services in these timeframes. The most common specialist services attended were rheumatology, haematology, physiotherapy and services relating to psychiatry, psychology or counselling (table 17).

Fifty three percent (n=312) of ever RNA positive and thirty two percent (n=89) of never RNA positive participants underwent one or more procedures. The vast majority were diagnostic in nature. Twenty eight percent (n=168) of ever RNA positive participants had a liver/abdominal ultrasound and this was by far the most common procedure (table 18).

The national hepatitis C database only contains information on specialist services and procedures if these are recorded in the patient's medical chart. If either are availed of privately and not discussed with the consultant hepatologist, they will be under-represented here. Services commonly attended on a private basis include counselling, physiotherapy, chiropody and complementary and alternative therapies.

Table 17. Most common specialist services, other than hepatology, attended between baseline and follow-up, or in the 12 months prior to baseline data collection (for new database participants)

Most common services attended	Ever RNA positive (%)	Never RNA positive (%)	All (%)
Rheumatology	49 (8.2)	34 (12.3)	83 (9.5)
Haematology	64 (10.8)	16 (5.8)	80 (9.2)
Physiotherapy	52 (8.8)	18 (6.5)	70 (8.0)
Psychiatry/psychology/counselling	52 (8.8)	6 (2.2)	58 (6.6)
Dermatology	39 (6.6)	12 (4.3)	51 (5.8)
Endocrinology	37 (6.2)	10 (3.6)	47 (5.4)
Surgical	33 (5.6)	13 (4.7)	46 (5.3)
Dietician/nutritionist	29 (4.9)	3 (1.1)	32 (3.7)
Nephrology	22 (3.7)	11 (4.0)	33 (3.8)
Cardiology	20 (3.4)	12 (4.3)	32 (3.7)
Obstetrics/gynaecology	19 (3.2)	6 (2.2)	25 (3.0)
Dental	16 (2.7)	2 (0.7)	18 (2.1)
Orthopaedic	13 (2.2)	5 (1.8)	18 (2.1)
Urology	11 (1.9)	4 (1.4)	15 (1.7)

Table 18. Most common procedures undergone between baseline and follow-up, or in the 12 months prior to baseline data collection (for new database participants)

Most common procedures	Ever RNA positive (%)	Never RNA positive (%)	All (%)
Ultrasound (abdomen/liver)	168 (28.3)	21 (7.6)	189 (21.7)
X-ray with barium/contrast (non-liver)	50 (8.4)	19 (6.9)	69 (7.9)
Diagnostic gastroscopy	42 (7.1)	13 (4.7)	55 (6.3)
CT Scan (site not specified)	43 (7.2)	11 (4.0)	54 (6.2)
X-ray (non-liver)	28 (4.7)	21 (7.6)	49 (5.6)
Colonoscopy	28 (4.7)	14 (5.1)	42 (4.8)
MRI (site not specified)	25 (4.2)	8 (2.9)	33 (3.8)
Ultrasound (non-liver)	23 (3.9)	10 (3.6)	33 (3.8)
Ultrasound (site not specified)	25 (4.2)	3 (1.1)	28 (3.2)
Mammogram	17 (2.9)	4 (1.4)	21 (2.4)
CT Scan (non-liver)	12 (2.0)	2 (0.7)	14 (1.6)
CT Scan (liver/abdomen)	8 (1.3)	2 (0.7)	10 (1.1)

Long term medications other than anti-viral treatment (for hepatitis C)

The most common long-term medications used were drugs for acid-related disorders, drugs used to treat depression, anxiety or sleep disorders, cardiovascular drugs and anti-inflammatory and anti-rheumatic drugs (table 19).

Table 19. Most common long-term medications recorded in medical charts

Medication type	Ever RNA positive (%)	Never RNA positive (%)	All (%)
Drugs for acid-related disorders	183 (23.2)	56 (12.6)	244 (19.1)
Psychoanaleptics	148 (18.9)	52 (11.7)	203 (15.9)
Psycholeptics	116 (14.8)	39 (8.8)	161 (12.6)
Beta blocking agents	107 (13.6)	37 (8.3)	145 (11.4)
Diuretics	95 (12.1)	36 (8.1)	131 (10.3)
Mineral supplements	97 (12.4)	33 (7.4)	130 (10.2)
Agents acting on the renin-angiotensin system	91 (11.6)	32 (7.2)	123 (9.6)
Serum lipid reducing agents	53 (6.8)	58 (13.1)	111 (8.7)
Anti-inflammatory and anti-rheumatic products	70 (8.9)	40 (9.0)	110 (8.6)
Analgesics	68 (8.7)	31 (7.0)	105 (8.2)
Anti-thrombotic agents	72 (9.2)	32 (7.2)	104 (8.2)
Drugs for treatment of bone diseases	72 (9.2)	25 (5.6)	97 (7.6)
Thyroid therapy	62 (7.9)	29 (6.5)	92 (7.2)
Sex hormones and modulators of the genital system	48 (6.1)	26 (5.9)	75 (5.9)
Antianemic preparations	51 (6.5)	16 (3.6)	72 (5.6)
Drugs for obstructive airway diseases	49 (6.3)	21 (4.7)	71 (5.6)
Calcium channel blockers	54 (6.9)	16 (3.6)	70 (5.5)
Drugs used in diabetes	50 (6.4)	16 (3.6)	67 (5.3)
Corticosteroids for systemic use	47 (6.0)	3 (0.7)	52 (4.1)

Chapter 5 Discussion

The National Hepatitis C Database was first developed in 2004. This report outlines the process of data collection, recruitment of new participants and the main findings of the first year of follow-up data collection.

Since baseline data collection, the participation rate has increased by 2% and now stands at 74.7%. The database contains a large amount of data on over one thousand people infected with hepatitis C in Ireland. Although all participants were infected through blood and blood products, they do not form a homogeneous group in many respects such as age at infection, sex, genotype and source of infection. However, these factors are taken into account in presenting the results.

A large proportion of database participants with chronic hepatitis C have now been infected for more than 25 years. International literature suggests that chronic hepatitis C disease progresses particularly between 20 and 30 years after infection, so this is now an important time to focus on outcomes and response to treatment through regular follow-up. Information about usage of services will also be helpful in predicting and planning for service needs in the future.

There is now evidence of significant disease progression in a proportion of those participants with chronic long-term infection, with 12% having developed cirrhosis. Apart from RNA status, high alcohol consumption was found to be the most important determinant of risk of cirrhosis and other adverse outcomes. Older age at infection, male sex, longer duration of infection and genotype 3 were also associated with poorer outcomes in database participants. Apart from the association with genotype 3, the other findings are in line with the published literature. The suggestion of poorer outcome for some genotype 3 patients will be followed closely in coming years.

We have now estimated the median time from infection to onset of cirrhosis in this group of patients (20.5 years) and have also estimated the annual rate of fibrosis progression. It will be interesting to follow these measures in the coming years to see if they hold true.

One very important outcome of the database so far has been the information on treatment responses. Although this information has been well published from international studies, the data presented in this report represent the true outcomes in an Irish population. Almost 40% of RNA positive participants have had one or more courses of anti-viral treatment. Treatment response in database participants has improved in recent years with the advent of combination therapy and is in line with the international experience, both in terms of the proportion achieving sustained virological response, and in the influence of age, genotype and type of treatment. Treatment response has been shown, both in this population and in studies in other countries, to be better in younger patients. Given the fact that the majority of untreated participants are now over the age of 50 years, response to treatment in this group may be lower in the future.

Limitations

In general, the quality of the information in the database is good. However, there are limitations, some of which we hope to improve in the future:

Older people were more likely to participate in the database, and data were collected on deceased people. This may have led to an over-estimation of disease progression. People infected through blood clotting factors are also under-represented in the database. However, the inclusion in this round of data collection of people who had died before the setting up of the hepatology units has resulted in improved representation of this group.

Spontaneous viral clearance rates may be overestimated if the whole database population is taken as the denominator, as some participants never had confirmed positive tests and a small number of these may

be false positive cases. For the anti-D and blood transfusion/renal groups, it is probably more accurate to calculate spontaneous clearance rates on the confirmed positive populations. For those infected through blood clotting factors, many had died before confirmatory tests were widely used and it is likely that most or all of the unconfirmed positive cases were true cases.

Date of infection was estimated for 28% of participants and the rules used for this are likely to have resulted in bias towards younger age at infection and longer duration of infection. This may have resulted in an under-estimation of the effects of age and duration of infection on disease progression. This is likely to have affected the groups infected through blood clotting factors more than the anti-D group.

Given the evidence for the impact of alcohol consumption on the progression of hepatitis C disease, it is unfortunate that there is not better information on alcohol available in the patient's medical charts. Most of the results on the relationship between alcohol and disease outcomes are based on analysis of alcohol consumption recorded at the first visit to the hepatology unit. Alcohol consumption is likely to be under-reported. This may explain why, although the results did demonstrate a relationship between high alcohol consumption and unfavourable outcomes, no such relationship was seen for moderately high consumption. It is important that accurate information about alcohol is recorded in a systematic way at routine clinic appointments.

To date, it has not been possible to investigate the influence of BMI on hepatitis C disease progression due to lack of BMI or height/weight data in most patient charts. This is an important area to investigate given the evidence in published literature for the relationship between BMI and disease progression.

As there is considerable variation in the recording of viral loads, to date it has not been possible to examine the relationship, if any, between viral load level and either disease progression or response to treatment. We hope to address this in the coming year.

The lack of a population-based comparison group limits the interpretation of some of the data, particularly that related to other medical conditions. A cross-sectional study is being planned to compare health, illness and lifestyle indicators in the hepatitis C database cohort with the general population using questions and data from large-scale standardised health surveys.

Recent developments to database

In 2007, the database was upgraded to a web technology based system, allowing the entry of data by the database research nurse to be completed on-site in the hepatology units. This method of data entry was piloted during the follow-up data collection but was found to be more time-consuming than manual entry onto a paper form, so paper-based data collection will be continued. However, having web-based access to the database in the hepatology unit was useful for the database nurse.

In 2008, a pilot study was carried out on electronic transfer of data from one hospital laboratory system directly into the database. Evaluation of this trial concluded that it resulted in little time-saving and the expense of rolling it out to the other seven hospital laboratories would not be justified.

The future of the hepatitis C database

The participation rate already achieved in this project is a tribute to the co-operation and support of the participants, support groups and staff in the hepatology units. It is our aim to continue to improve this rate by encouraging non-responders to join now. A higher participation rate will mean that the data will more closely reflect the entire hepatitis C population infected through blood and blood products in Ireland. For eligible 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 clinical staff. In addition, the four patient support groups are committed to the project and will continue to encourage their members to join as opportunities arise.

The lack of standardisation of data recording in two areas has given rise to difficulties – liver biopsy scoring and viral load measurement. We hope to resolve these issues in the coming year so that optimum use can be made of this information.

We also hope to improve recording of data in two key areas – BMI and alcohol consumption. Both of these factors are known to be key determinants of hepatitis C disease progression. Recent data on both is essential in accurately assessing their impact so we would encourage clinical staff to attempt to record these at routine out-patient visits.

The data in the database are available for use by researchers and by the participating hepatology units. The policy and procedures for accessing information contained in the database are outlined in a document which is available on the database website or through the project team at HPSC. All publications based on data from the database must acknowledge the National Hepatitis C Database and the participating hepatology units.

The annual collection of data on participants will continue. The type of data collected each year may be modified as new questions arise or new developments come to light. Regular reports will be produced with a focus on health outcomes, treatment response and service usage. This information will be of value in planning health service provision for the future, and may facilitate individuals and healthcare professionals in relation to health and lifestyle decisions such as alcohol consumption and the timing of anti-viral treatment.

Finally, we would welcome any comments and suggestions that participants, health professionals or other interested people may have on ways in which we could improve the database and the use of the information contained in it.

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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 RNA (PCR), line-immunoassay (RIBA/INNO-LIA) or EIA results, indeterminate line-immunoassay results and weak positive EIA results.

Confirmed positive case of hepatitis C
Any patient who had at least one positive RNA(PCR) result or at least one positive line-immunoassay (RIBA/INNO-LIA) result.

Ever hepatitis C RNA positive (PCR positive)
Any patient who had at least one positive RNA(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.

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.

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 to 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.

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.

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.

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

ALT	Alanine aminotransferase (a liver enzyme)
Anti-HCV	Antibody to hepatitis C virus
EIA	Enzyme immunoassay, a screening test for hepatitis C
HAA	Health (Amendment) Act
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
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
NDSC	National Disease Surveillance Centre, now known as the Health Protection Surveillance Centre
NICE	National Institute for Clinical Excellence
PCR	Polymerase chain reaction
RIBA	Recombinant immunoblot assay, a more specific hepatitis C test
RNA	Ribonucleic acid
WHO	World Health Organization

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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

Database News

Newsletter of the National Hepatitis C Database Issue 1 February 2008

Contents

hpsc

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Database website:
www.hcvdatabase.ie

Pictured at the launch of the Hepatitis C Database Report were Eleanor O'Mahony, Positive Action; Michele Tait, HSE; Noeleen White, Positive Action; Margaret Dunne, Irish Haemophilia Society; Lelia Thornton, HPSC; Minister Mary Harney; Liz Kenny, Consultative Council on Hepatitis C; Maura Long, Transfusion Positive.

Welcome to Database News

Welcome to the first edition of *Database News*, the newsletter of the National Hepatitis C Database. Our aim is to keep you up to date on everything that is happening with the database.

Special thanks are due to everyone who has taken part in the database, as it provides important information on hepatitis C. It gives information about the natural history of infection and allows us to look at the progression of the disease. It will also highlight the response to treatment, help in the planning of health services and serve as a resource for future research into hepatitis C.

The database contains medical information about people who were infected with hepatitis C by blood or blood products in Ireland. All information is anonymous, therefore the database does not contain names or addresses of patients.

All the hepatology units around the country have given great support to the database since 2004 when work on the project started. We are grateful to the staff in St James's, Beaumont, Our Lady's Hospital Crumlin, the Mater, St Vincent's, St Luke's Kilkenny, University Hospital Galway and Cork University Hospital for their help.

How the database came about

In 1996, the Consultative Council on Hepatitis C was set up to advise the Minister for Health on all matters relating to hepatitis C. The Council's first review of services was published in March 2000 and one of its recommendations was to set up a database to learn more about the disease and its effects on patients.

The Health Protection Surveillance Centre (HPSC), Ireland's specialist agency for infectious disease surveillance, was chosen to set up and take care of the database. HPSC works closely with the hepatology units around the country.

Everyone infected by blood and blood products can take part in the database

Everybody who has been infected with hepatitis C by blood and blood products administered in Ireland can participate at anytime, says Project Coordinator, Dr Lelia Thornton.

"Anybody who has ever attended any of the eight designated hepatology units has already been invited to take part. People who have not yet agreed to take part can still participate by contacting their hepatology unit or any of the hepatitis C patient support groups.

"To get a full picture it is really important that as many people as possible participate in the database," she added.

What information is collected in the database?

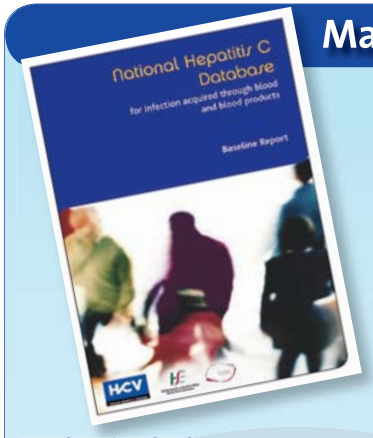
Information is collected on people who agree to participate in the database and on people who have died.

As data is taken from the patient's medical records in the eight hepatology units, there is no need to contact patients. Patient names or addresses are not recorded in the database. The information collected includes details of the source of the hepatitis C infection, current state of health, attendance at health services, liver biopsy and other test results, and treatment information.

A research nurse from HPSC collects the data. Information from the first round of data collection - which goes back over the years to the time of diagnosis – has now been published, and is available at www.hcvdatabase.ie. If you haven't already received a copy of this report then contact your hepatology unit, liaison officer or support group.

Follow up on participants has already started, and will be completed on a yearly basis - allowing us to monitor the progression of disease in the group.

Main findings from first data collection



Numbers involved

- Over 1,600 people have been infected with hepatitis C virus through contaminated blood or blood products in Ireland.
- The database contains information on 1,192 of these patients.

Sources of infection

Of the 1,192 participants

- 770 or 65% were infected by anti-D immunoglobulin.
- 284 or 24% were infected by blood transfusion.
- 107 or 9% were infected by treatment for blood clotting disorders.
- 25 or 2% were infected by treatment for kidney disease, including blood transfusion.

Description of participants

- Older age groups were more likely to participate.
- Over 80% of the 1,192 participants are female, reflecting the large group infected through anti-D immunoglobulin.
- The average age at infection was 28 years but varied by source of infection.
- 76% of the group 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.

Hepatitis C results

- 63% had tested PCR positive at some time, indicating active infection.
- Of those tested for genotype, three quarters of all participants, and 90% of the anti-D group, were genotype 1. Genotype 1 is associated with a less successful response to anti-viral treatment.

Alcohol

- 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.
- Patients who consumed alcohol in excess were more likely to have moderate or severe inflammation on liver biopsy, to have high fibrosis scores and to have cirrhosis.

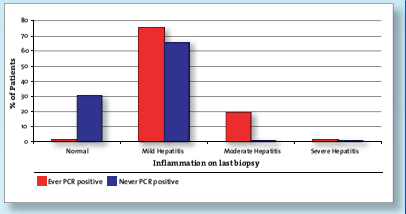
Clinical condition

- The most commonly recorded medical 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.
- Without a comparison group, it is not possible to say if the prevalence of these conditions is different from the general population. Also, these conditions are not necessarily diagnosed according to standardised criteria, and they may be unrelated to hepatitis C infection.

Liver biopsies

- Of patients who tested PCR positive and had a liver biopsy, 77% had mild inflammation, 20% had moderate inflammation and 2% had severe inflammation.
- Patients who consumed alcohol in excess were infected for longer and were older, and they were significantly more likely to have moderate or severe inflammation.
- High fibrosis scores on liver biopsy were less prevalent in the anti-D group (8%) than in the blood transfusion (28%), blood clotting disorder (21%) or renal (20%) groups.
- Patients infected by blood transfusion were more likely to have cirrhosis of the liver than those infected by any of the other routes.

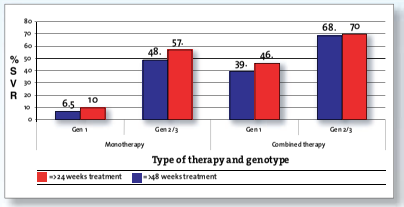
Source of infection	% of patients with cirrhosis	% of ever PCR positive patients with cirrhosis
Anti-D	3.4	6.1
Blood transfusion	13.7	16.9
Blood clotting disorders	6.5	8.2
Renal	8.0	8.3
Total	6.2	9.7



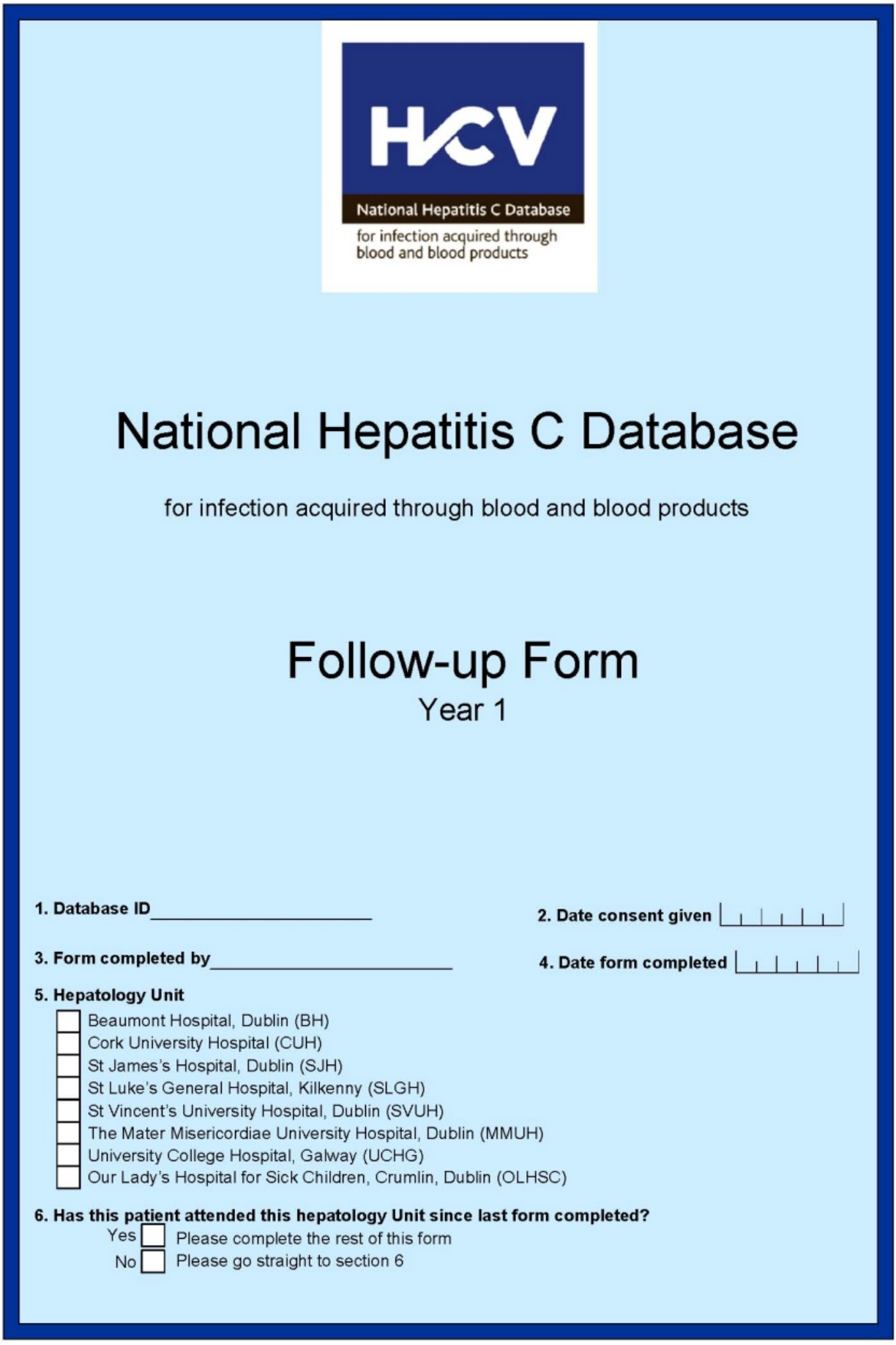
Treatment

- The data shows that only 37% (276 patients) who tested PCR positive had ever received anti-viral treatment to date.
- Patients with genotype 2 or 3 responded better to treatment. This was also seen in patients who received combination therapy (treatment with more than one drug), who were under 45 years old when treatment started, who received treatment for a longer time or who were infected for less than 20 years.

The graph below shows the response (sustained viral response) to the first course of treatment, by duration of treatment and genotype, for patients on monotherapy (one drug) and combination therapy.



Appendix D Data collection form for first year of follow-up



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

National Hepatitis C Database

for infection acquired through blood and blood products

Follow-up Form

Year 1

1. Database ID_____ **2. Date consent given** |_|_|_|_|_|_|

3. Form completed by_____ **4. Date form completed** |_|_|_|_|_|_|

5. Hepatology Unit

- ☐ 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 Hospital, Galway (UCHG)
- ☐ Our Lady's Hospital for Sick Children, Crumlin, Dublin (OLHSC)

6. Has this patient attended this hepatology Unit since last form completed?

Yes ☐ Please complete the rest of this form
No ☐ Please go straight to section 6

Database ID _____ Date last form completed | | | | | | |

Section 1. Patient Details

7. Patient initials | | | **8. DOB** (dd/mm/yy) | | | | | | **9. Height** _____ **10. Weight** _____

11. County of residence _____ **12. Occupation (as recorded in medical records)** _____

13. Birth history (*if female*) Number of pregnancies since last form completed _____

Number of live births since last form completed _____

14. Alcohol intake at last visit (*units/week*)

Females / Males	Non-Drinker	<=14 / <=21	15-40 / 22-40	>40 / >40
	☐	☐	☐	☐

15. Smoking status at last visit (*cigarettes/day*)

Non-Smoker	1-20	>20
☐	☐	☐

16. Patient's death recorded since last form completed? Yes ☐ No ☐ If yes: date of death (dd/mm/yy): | | | | | |

cause of death _____

17. Other significant viral infection(s) (diagnosed since last form completed)? Yes ☐ No ☐

If yes, please specify _____

18. Other known liver disease (diagnosed since last form completed)? Yes ☐ No ☐

If yes, please specify _____

19. Other significant medical conditions (diagnosed since last form completed)? Yes ☐ No ☐

If yes, please specify _____

Section 2. Clinical Status

20. Signs of HCV related liver disease (diagnosed since last form completed)

Yes ☐ No ☐

If yes, please specify below

- ☐ Ascites
- ☐ Varices
- ☐ Bleeding varices
- ☐ Liver tumour/HCC
- ☐ Encephalopathy
- ☐ Other (please specify) _____

21. Extrahepatic manifestations of HCV infection (diagnosed since last form completed)

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

22. Date of most recent visit for HCV related care (dd/mm/yy) | | | | | |

23. Hepatology related care since last form completed

☐ 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

24. Procedures undergone since last form completed

Procedure	No. of times
☐ Diagnostic gastroscopy	_____
☐ Therapeutic banding gastroscopy	_____
☐ Therapeutic injection gastroscopy	_____
☐ TIPPS	_____
☐ Ultrasound	_____
☐ CT	_____
☐ MRI	_____
☐ Hepatic angiography	_____

Other, specify procedure and number of times _____

Please specify type of ultrasound _____

25. Other medical/surgical/psychiatric services attended (since last form completed)

_____

26. Other specialist healthcare services (including physiotherapy & dental) attended (since last form completed)

_____

Database ID _____ Date last form completed ☐☐☐☐☐☐

27. Liver transplant recipient (since last form completed) Yes ☐ No ☐

If yes, Date (dd/mm/yy): ☐☐☐☐☐☐ If no, have they been put on the waiting list? Yes ☐ No ☐

Are they currently on the waiting list? Yes ☐ No ☐

Section 4. Test Results

28. Liver function tests (LFTs) (most recent)

Date (dd/mm/yy) ☐☐☐☐☐☐

Results: ALT _____ INR _____ PTR _____

AST _____ AFP _____

Bilirubin _____ Alk Phos _____

Albumin _____ Gamma GT _____

29. RIBA (*please record banding pattern of most recent OR if banding not available record results as pos/neg/ind*)

Date (*dd/mm/yy*) ☐☐☐☐☐☐ C100 ___ C33 ___ C22 ___ NS5 ___ OR Pos. ☐ Neg. ☐ Ind. ☐

30. HCV PCR (ALL since last form completed)

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

31. HCV genotype/sequence information:

Genotype/subtype _____

Sequence information ☐ 1977 ☐ 1991

32. HLA type

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

33. Autoantibodies (*most recent*)

Date (dd/mm/yy) ☐☐☐☐☐☐

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

34. Liver biopsy Yes ☐ No ☐ If yes, give details of ALL since last form completed below:

Laboratory reference no.	Date of biopsy (dd/mm/yy)	Chronic hepatitis: Normal	Mild	Moderate	Severe	Fibrosis score	Scoring system	Cirrhosis	HCC
_____	☐☐☐☐☐☐	☐	☐	☐	☐	_____	_____	☐	☐
_____						_____	_____		

Section 5. Treatment

35. Anti-viral treatment for HCV (since last form completed) Yes ☐ No ☐ If yes, please give details of ALL below

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

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

36. 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

37. Drug trial participation (since last form completed)

Yes ☐ No ☐

If yes, details _____

Section 5. Treatment

38. 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

Appendix E Biopsy Scoring

Table 20. Fibrosis scoring systems

Score	Original HAI or Knodell[19]	Modified HAI or Modified Knodell or Ishak[20] or Desmet[21]	Scheuer[22]	International group of Hepatopathologists*
0	No fibrosis	No fibrosis	None	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
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
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)
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
5		Marked bridging with occasional nodules (incomplete cirrhosis)		
6		Cirrhosis, probable or definite		

The grade of inflammation on biopsy was categorised as:
Normal, mild inflammation, moderate inflammation or severe inflammation

Appendix F 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,
Email Address : transfusionpositive@eircom.net, Website : www.transfusionpositive.ie

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
Mr Larry Bathe, Health Service Executive, Mill Lane, Palmerstown, Dublin 20. Tel: 01 620 1758

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,, 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
Mr Richard Broderick, Health Service Executive Primary Carue Unit, Merlin Park Regional Hospital, Galway. Tel: 091-775923

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@hse.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
Email: info@consultativecouncilonhepc.ie, Website: http://www.consultativecouncilonhepc.ie

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on behalf of the Consultative Council on Hepatitis C

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