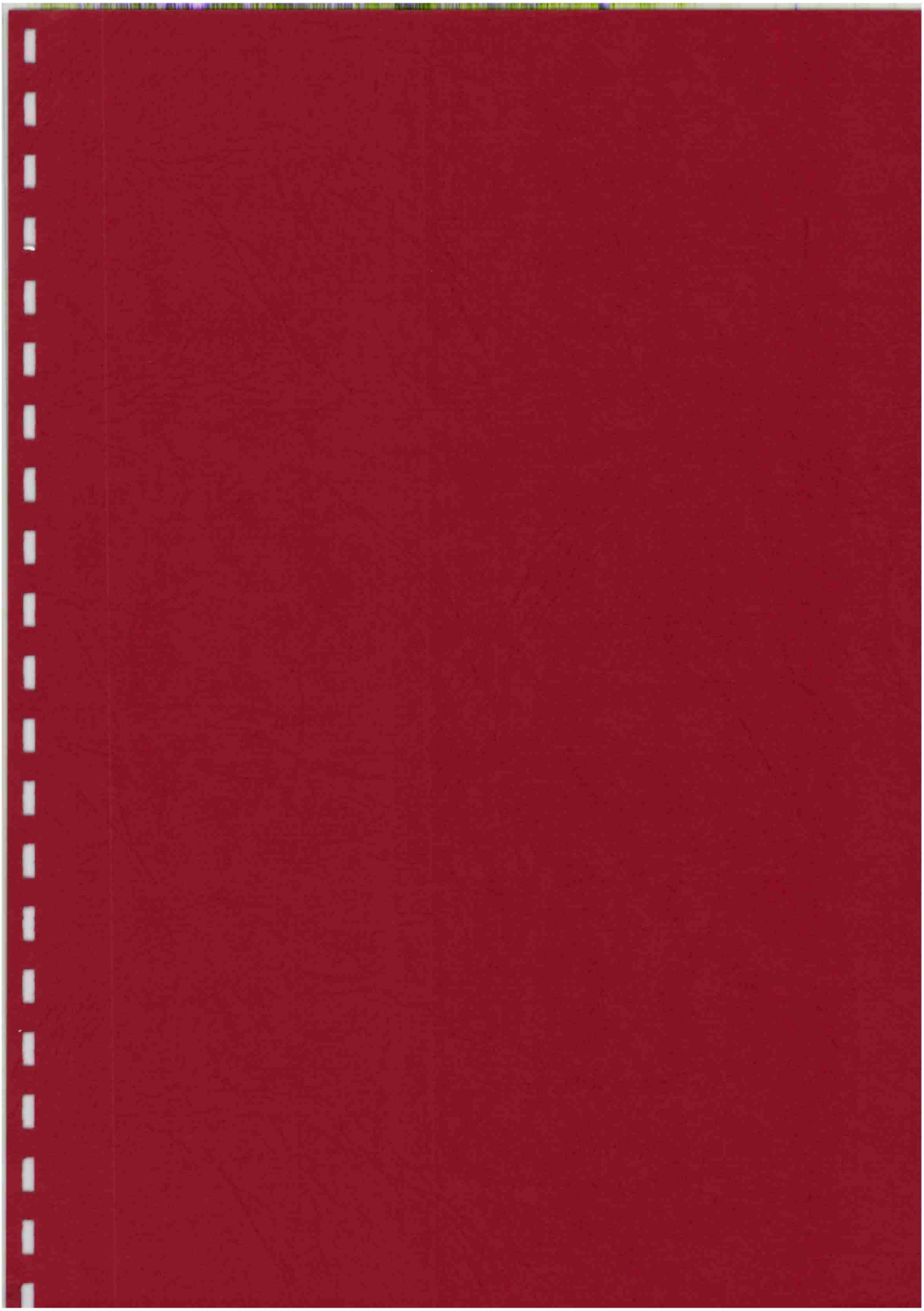

NATIONAL REGISTER HCV

NATIONAL REGISTER OF HCV INFECTIONS

WITH KNOWN DATES OF INFECTION

FINAL REPORT

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on behalf of the HCV National Register Steering Group

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CONTENTS

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1.0 EXECUTIVE SUMMARY

The report describes the development of the National Hepatitis C Register and the completeness of the data it contains. A description of the structure and function of the Register, including case definitions, registration and follow-up procedures, and methods used to maximise data quality and to obtain comparative data sources are given.

The Register contains data on HCV-infected individuals who acquired their infections on a known date and by a known route. To date, the majority of cases are transfusion recipients identified during the UK lookback exercise, who tested positive or indeterminate for anti-HCV after receiving 'infected' blood issued before the introduction of routine testing of the blood supply for anti-HCV. By 31 December 1999, 871 (87%) of 996 eligible transfusion recipients had been registered, and 984 (99%) flagged in the NHS Central Registers. Registered patients had been infected for an average of 11.1 years (SEM 0.1); around half were being cared for by clinicians with a specialist interest in liver disease. Except for the information on tobacco use; current alcohol use, and hepatitis B status, data were more than 80% complete, and for most variables, more than 90% complete. The consistency of data abstraction was found to be 98% (SEM 0.5).

The Register contains high quality anonymised data on one of the largest cohorts of individuals with HCV infections acquired on a known date and by a known route. It could serve as a model for other chronic disease registers; developers may find the structure, design, and methodological issues addressed useful.

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The data contained in the Register have been analysed to inform the natural history of hepatitis C virus (HCV) in the first decade of infection. This national cohort study included 927 HCV infected transfusion recipients traced during the HCV lookback programme, and 475 anti-HCV negative transfusion recipients (controls). The main outcome measures investigated were clinical evidence of liver disease, and survival after 10 years of infection.

All-cause mortality was not significantly different between cases and controls (hazard ratio of 1.41, 95% CI 0.95 – 2.08). Cases were more likely to be certified with a liver-related death (hazard ratio 12.8, 95% CI 1.73-95.4), but although the risk of death from liver disease was higher in cases than controls this difference was not statistically significant (hazard ratio 5.78, 95% CI 0.72-46.6). One third of the cases who died from their liver disease were known to have consumed excess alcohol. Clinical follow-up of 829 cases showed liver function to be abnormal in 307 (37%) and 115 (14%) reported physical signs or symptoms of liver disease. Factors associated with developing liver disease were HCV ribonucleic acid positivity (odds ratio 6.44 95% CI 2.67-15.5), transfusion when older (Age ≥ 40 years; odds ratio 1.80, 95% CI 1.14 - 2.85), and years since transfusion (odds ratio 1.096, 95% CI 1.00-1.20). For those with severe disease, sex (Female odds ratio 0.38, 95% CI 0.17-0.88) was also significant. Of the 362 who had undergone liver biopsy, 326 (90%) had abnormal histology: 35 (10%) of these were cirrhotic.

Overall, HCV infection did not have a great impact on all-cause mortality in the first decade of infection. Infected individuals were at increased risk of dying from a liver-related cause, particularly if they consumed excess alcohol, but this difference was not formally significant.

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2.0 PROJECT AIMS

The principal objectives of the national register are described below:

2.1 To describe the current biochemical, histological and clinically apparent liver disturbance in cases of HCV infection, and to relate current status to the interval since presumed infection and other potential prognostic factors.

Information on natural history is needed to help determine the current and future burden of hepatitis C related disease on health care services, and to assess the impact of currently available treatments as well as those that may become available in the future. Although complete information will only become available after many years of follow-up, baseline and short term follow-up information collected during the period of establishment will help to ascertain the early outcome of infection, to provide prognostic information to patients and to inform shorter-term health service planning. Death data will provide information on any HCV-related mortality that may result.

2.2 To monitor the number of known new infections

Extension of the register to include categories other than transfusion acquired HCV will provide information on trends in numbers of new infections in the UK. As the register will contain only individuals with a 'known date' of infection, it may not provide an unbiased estimate of such trends since changes in testing patterns may affect the numbers identified even in the absence of any true change in incidence. However, given the limitations and expense of other methods, the register will make a useful contribution to existing knowledge.

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2.3 To provide a shared national resource for use by those designing future studies

A number of future studies can be envisaged which would benefit from linkage with, and access to, the register. These include studies of sexual, vertical and household transmission; clinical trials of new antiviral drugs; further evaluation of existing antivirals and of alternative treatment protocols; determination of the relationships between viral load, genotype, treatment and disease progression; and study of markers prognostic for progression to disease.

2.4 To determine the representativeness of the registered population in relation to the total population of HCV infection in the UK

Although infected patients identified during the lookback exercise will form a unique cohort of individuals, the usefulness of the data generated will depend upon how representative this group is of the total population of HCV infected individuals. This information will help to establish the appropriate resources for future follow-up of this group and the future recruitment of patients to the register.

2.5 To pilot methods for recruitment, tracking and longer-term follow-up of this cohort.

Establishment of the register will require the ability to identify the appropriate clinician to contact, to gain the co-operation of that clinician and to access suitable baseline information. This pilot will help to determine mechanisms that maximise response rate, compliance, and completeness of clinical information. This process will inform the conduct of any future follow-up and establish what future resources will be required.

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3.0 METHODS

The HCV National Register: towards informing the natural history of hepatitis C infection in the UK

3.1 Introduction

Hepatitis C virus (HCV) is one of the most common causes of liver disease,[1] and is a major health problem worldwide.[2] Since both the acute and chronic phases of HCV infection illnesses are predominantly asymptomatic, and because the chronic illness runs a course measured in years rather than months, it has been difficult to define the frequency and rate at which infection progresses to symptomatic or end-stage liver disease.

Much of the current information about the natural history of HCV infection has been accrued from studies of patients with established chronic liver disease.[3] Unfortunately, such studies exclude individuals with clinically inapparent infection and those who have clinically apparent liver disease but have not been tested for HCV. This approach inevitably biases the data in favour of more severe disease outcomes. There is therefore a need for other studies that allow a more complete description of the spectrum of HCV-related disease by following cases from the date of infection onwards.

When anti-HCV testing of donated blood was introduced in the United Kingdom in 1991, some of the anti-HCV positive donors identified had donated blood before the introduction of testing. In early 1995, the UK Health Departments announced that a 'lookback' at recipients of blood or blood components derived from these donations would be undertaken.[4] Recipients

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were identified from local hospital records, and those who were not known to have died were contacted and offered counselling, serological testing, and treatment for HCV infection, if appropriate. These individuals may have experienced other exposures to infection but for most found to be anti-HCV positive, their most probable route of infection has been assumed to be transfusion. Cases of transfusion acquired HCV infection are unusual in having a known date of acquisition, an identifiable source, and often, in having been identified relatively early in the course of infection by a process largely unrelated to any HCV disease progression. As a consequence of the exclusion of HCV-infected donors from the donor panel, the incidence of transfusion acquired HCV in the UK has fallen to the extent that such infections are now uncommon. Thus, the patients who were traced during the HCV lookback form a rare cohort, offering an unrepeatable opportunity to study the natural history of HCV infection in the UK.

In response to this, we set up the National HCV Register. The aim of this paper is to describe the development of the Register, and assess the completeness of the data contained within it at the end of December 1999.

3.2 Methods

3.2.1 Registration

An individual who satisfied the following case definition was eligible for inclusion: 'A transfusion recipient traced during the HCV lookback exercise who tested either positive or indeterminate for antibodies to HCV.'

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The UK Blood Services invited clinicians, by letter, to register their eligible patients (Fig. 1). The process by which patients were initially traced, tested and referred for specialist HCV-care during the national lookback programme has been reported elsewhere.[5] The clinicians were asked to provide anonymised information on the patients' clinical status, test results, treatment and management (Table 1) using a standard form (see section 6.0 appendix). Any available clinical data for patients who had died were also collected. Clinicians caring for a large number of eligible patients were offered assistance with completion of their forms. Registered patients were 'flagged' in the NHS Central Registers[6] for notification of death, cancer and movement within or between health authorities.

Each registered patient has been given a unique case reference number. Registration data, which were entered twice to eliminate data entry errors, are stored in a series of related tables linked by the unique case reference number within a commercially available database (Access 97; Microsoft® Corporation Inc., Washington, USA). These data are linked to tables storing infection data on all patients who were traced, counselled and tested as part of the HCV lookback programme. Data on registrations of cancer or death from the NHS Central Registers are also stored within the database, including the full text of death certificates with contributory and underlying causes of death coded to the 9th revision of the International Classification of Diseases (ICD9).[7]

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Table 1. Data collected at registration (data in italics will also be gathered at the time of follow-up)

Variable	
Patient details	Date of Birth Sex Ethnic group Country of birth *Current*/past *smoking status* *Current*/past *alcohol consumption* Other risk factors for HCV infection Other significant chronic viral infections Significant medical conditions
Current clinical status	*Clinical evidence of liver disease (none, HCV-related liver disease, non-HCV-related liver disease)* *Signs and symptoms of liver disease (spider naevi, hepatomegaly, splenomegaly, ascites, varices, liver tumors and others)*
Test results	Hepatitis B status (HBsAg, anti-HBc) *HCV RNA status* *Liver function (AST, ALT, Bilirubin, Albumin)* *Results of liver biopsy*
Antiviral drug treatment	*Details of anti-viral treatment (dose, preparation, schedule, duration, and response)* *Participation in antiviral drug trials*
Current management	*Details of HCV-related care (none, outpatient, inpatient-assessment, inpatient-medical care)*

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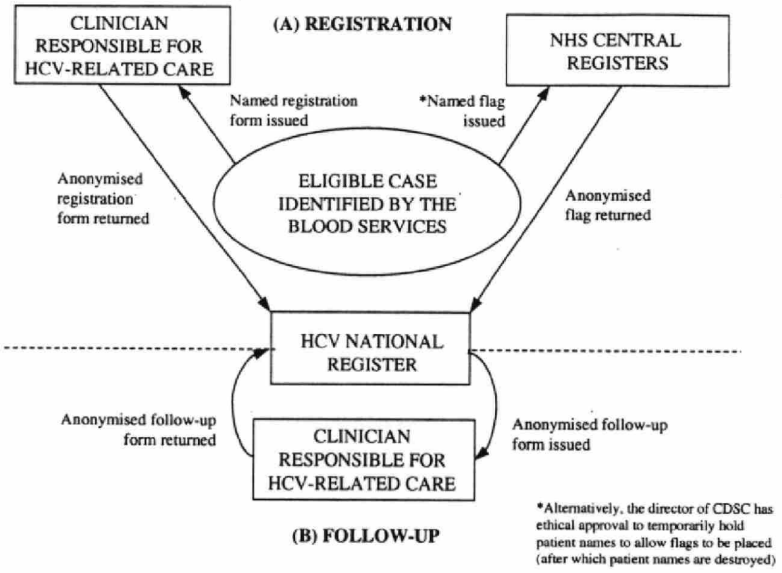
Fig. 1 Procedures for registration, flagging and follow-up.



To assess the consistency of data abstraction in the larger clinical centres, 2 independent observers (HEH, KE) each abstracted 88 data points from 20 sets of medical notes. The consistency of data abstraction was expressed as the mean percentage agreement between observers (Percentage agreement = N / 88 * 100, where N = number of variables abstracted correctly by both observers).

3.2.2. Comparative data sources

Due to ethical, feasibility, resource and power considerations, an ideal control group for analytical purposes is not available. To provide a source of data on HCV-negative transfusion recipients, all patients from the HCV lookback exercise in England who were traced, counselled, and who tested negative for anti-HCV have been flagged within the NHS Central Registers. This will enable us to compare deaths in this group from all causes, and from

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specific liver diseases, with those of registered cases. Routinely collected death data from the general population,[8] which includes deaths due to hepatocellular carcinoma and to other chronic liver disease, will also be used as a comparator.

3.2.3. Follow-up

Registered cases are followed up annually. A standard form (see section 6.0 appendix), identifying the patient by the unique case reference number and the clinician's own identifier, is sent directly to the relevant clinician, who provides data on current clinical status, test results, treatment and management (italics, Table 1). The form can be expanded to collect data required for research projects being supported by the Registry.

3.2.4. Central archive of sera and liver biopsy sections

There may be considerable inter-observer variation in interpretation of liver histology,[9] particularly when pathological changes are minimal. To reduce this, clinicians will be invited to send sections of liver biopsy specimens from their patients to the Registry, where they will be reviewed by two independent histopathologists and subsequently archived. A central archive of sera specimens, stored at –80°C, will also be established to serve as a national resource. Initially, specimens will be used to determine HCV genotypes. Future uses might include, for example, investigation of putative markers of disease progression.

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3.2.5. Applications to access Register data

One of the Register's main objectives is to serve as a national resource for use by researchers. A number of studies that would benefit from access to, or linkage with, the Register can be envisaged. These might include studies of sexual, household, or vertical transmission; evaluation of existing or future antiviral drugs; determination of the relationships between genotype, treatment and disease progression, and studies of markers prognostic of disease progression.

To fulfil this objective, a call for study proposals is issued annually.[10] The Register Steering Group reviews all applications and authorises the appropriate use of Register data in other studies. All applicants are required to obtain ethical approval for their proposed studies.

3.2.6. Confidentiality

No patient names are recorded within the Registry database. Data, including non-nominal identifiers, are securely stored on a password-protected computer within a secure building, and are accessible only to key individuals. Data sets passed to external researchers, whose projects are being supported by the Registry, contain no information that could lead to identification of registered patients. As the Register collates anonymised information that is collected by clinicians during routine patient care, and requires no special intervention, there is no formal requirement to gain patient consent. The PHLS and North Thames Multi-Research Ethics Committees have approved Registry protocols and Caldicott guidelines have been adhered to.

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3.3 Results

3.3.1. Registration

Clinicians have returned completed registration forms for 871 (87%) of the 996 eligible transfusion recipients in the UK who were traced during the HCV lookback exercise. Virtually all recipients (984; 99%) have been flagged in the NHS Central Registers; the remaining 12 have returned to countries outside the UK.

The consistency of data abstraction from medical notes was found to be 98% (SEM 0.5, range 93–100). Disagreements occurred in 2% of data points, on average. Ranked in descending order of importance, these resulted from: (1) failure to find the information; (2) transcription error; (3) differing interpretations of subjective terms, usually related to patients' tobacco or alcohol use; (4) differing views on whether an unrecorded symptom/ sign should be assumed to be absent; (5) confusion of dates of sampling with dates of testing or of reporting; (6) misinterpretation of reported fibrosis scores; (7) inconsistencies or ambiguities within the medical notes.

3.3.2. HCV negative transfusion recipients

Of 536 English transfusion recipients who tested anti-HCV negative in the lookback exercise, 532 (99%) have been successfully flagged. Four could not be flagged: two had returned to countries outside the UK; two could not be traced.

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3.3.3. Profile of registered transfusion recipients

At the end of 1999, the mean time since 'exposure' to HCV among the registered cases was 11.1 (SEM 0.1) years. The infection status of these cases is summarised in Table 2. One hundred and eight are known to have died. At registration, approximately half (52%) of the patients were being cared for by a clinician with a specialist interest in liver disease (gastroenterologists, 35%; hepatologists, 7%; infectious disease physicians, 7%; paediatric hepatologists/gastroenterologists, 2%). The other patients were being cared for either by their general practitioner (24%) or by a clinician from one of a variety of other specialities (24%). The median age of the cases at the time of transfusion of the implicated donation was 45.8 years (Mean = 43.6 years, SEM 0.7); their age/sex profile is shown in Fig. 2. Most cases were born in the UK, and most are white.

3.3.4. Completeness of data in the Register

The completeness of registration data is summarised in Table 3. Date of birth, sex and date of 'infection' are known for all registered cases. With the exceptions of past and current tobacco use, current alcohol use, and hepatitis B status, the data are more than 80% complete, and for many variables, more than 90% complete. Current alcohol consumption was known for 65% of the patients who reported consuming *any* alcohol when they were first seen, but was only known for 35% of the patients who reported their alcohol consumption to be nil when they were first seen ($\chi^2 = 14.6$, $P < 0.001$).

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Table 2. Infection status of the 871 registered patients at the time of initial HCV testing

Infection Status	EIA result	RIBA result	HCV PCR result	N
Infected	Positive	Positive	Positive	373
	Positive	NK	Positive	142
	Positive	Positive	NK	110
	Positive	Positive	Negative	101
	Positive	Indeterminate	Positive	14
	NK	NK	Positive	9
	Negative	Negative	Positive	5
	NK	Positive	Positive	5
	Negative	NK	Positive	5
	Indeterminate	Indeterminate	Positive	4
	Indeterminate	Positive	Negative	2
	NK	Positive	NK	2
	Positive	Positive	Indeterminate	2
	Negative	Indeterminate	Positive	1
	Positive	Negative	Positive	1
Indeterminate	Positive	Indeterminate	Negative	38
	Negative	Indeterminate	Negative	12
	Indeterminate	Indeterminate	Negative	10
	Indeterminate	Indeterminate	NK	1
Not known (insufficient)	Positive	NK	NK	17
	Positive	NK	Negative	13
Reactive (confirmed neg.)	Positive	Negative	Negative	4
TOTAL				871

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Figure 2. Age/sex profile of registered HCV lookback recipients at the time of receiving 'infected' transfusion.

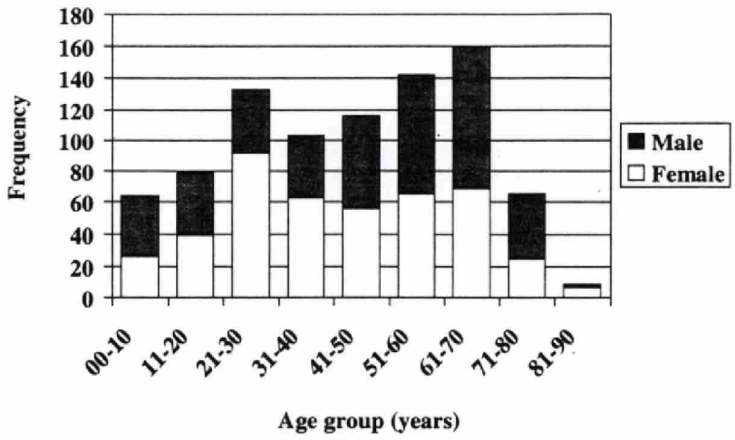

Table 3 Completeness of registration data (n = 871, of whom 108 are known to be dead)

Variable	% known	% known after excluding deceased
Date of Birth	100	100
Sex	100	100
Ethnic group	92	93
Country of birth	89	90
Current (ever-) smoking	65 (62)	70 (67)
Current (past-) alcohol consumption	54 (86)	58 (87)
Risk factors for HCV infection: IDU (other)	87 (95)	89 (95)
Other significant chronic viral infections	96	99
Significant medical conditions	97	99
Clinical evidence of liver disease	91	97
Signs and symptoms of liver disease	91	97
Hepatitis B status: HbsAg (anti-HBc)	41 (73)	42 (74)
HCV RNA status	90	92
Normality of liver function	92	94
Liver biopsy details	93	98
Details of anti-viral treatment	95	99
Participation in antiviral drug trials	83	88
Details of HCV-related care	94	99

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3.3.5. Applications to access Register data

The Registry is supporting an international research project based in Edinburgh. Data sets derived from registration and follow-up data are being provided to the group to enable them to train and validate an artificial neural network that uses viral and clinical factors to predict cirrhosis in patients with chronic HCV.[11]

3.4 Discussion

It is difficult to design and undertake studies that can convincingly define the natural history of HCV infection. An ideal study would, as Seeff proposed, (1) accurately define the onset of infection, (2) identify and evaluate the full spectrum of disease rather than focussing on severe illness, (3) track the infection from onset either to resolution, the development of end stage disease, or death, (4) evaluate the outcome without instituting treatment that might modify the course, and (5) assemble a properly matched uninfected control group which could be followed with the same zeal and intensity as the infected cohort.[12]

Seeff acknowledged that it would be difficult, if not impossible, to meet these requirements,[12] but these criteria serve as a *gold standard* against which studies can be measured. By including only those infections with a known route and date of acquisition, the HCV National Register fulfils the first two criteria, and unlike other studies has the advantage of including cases of both sexes,[13-15] and of including infections acquired from virologically different sources.[13; 14] It hopes to meet the third criterion by following all registered cases until death, although some loss to follow-up prior to registration may have occurred. By flagging patients

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in the NHS Central Registers, we hope we have ensured that, even if reporting compliance falls, or the intensity of follow-up cannot be maintained, it will, as a minimum, be possible to establish the cause of death for every registered case. The fourth criterion is indeed difficult to meet. Treatment of chronic HCV infection, either with interferon alone, or with more effective antiviral combination therapies,[16; 17] is becoming increasingly common,[18] which means that it would be both unrealistic and unethical to expect to preserve a cohort of untreated patients. Nevertheless, by collecting full details of all treatment, it should be possible for us to control for differences in treatments between individuals, and to evaluate the long-term outcomes of different treatments.

Meeting the final criterion (recruitment of a suitable control group) is less than straightforward. It would not be feasible – and might be unethical – to follow a control group as intensively as registered cases, and mortality data are therefore likely to provide the most reliable comparator of outcome. Choosing a control group is difficult, since it is not immediately apparent which group would be the most appropriate. To date, all of the registered cases have acquired their HCV infections by transfusion, and transfused patients are known to have a high mortality. Without a control group of similar, but uninfected, patients, mortality could be wrongly attributed to HCV, and the adverse outcomes of HCV infection overestimated. We therefore decided to obtain specific and all-causes mortality data for comparison, by flagging patients who were traced during the HCV lookback exercise but who tested negative for anti-HCV. This group of patients is similar to the registered cases, since all have been transfused, were traceable by the same mechanism, and survived long enough after transfusion to be tested. In addition, information is available on a number of potential confounding factors (e.g. anti-HBc status and alcohol consumption). On the other hand, these patients are anti-HCV negative despite being recorded as having received a

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transfusion from a donor later found to be anti-HCV positive. The reason for this could be that the donor was not infected, or infectious, at the time of donation; that the patient did not actually receive the unit as recorded; that the patient received an infectious unit but did not become infected, or that the patient became infected but subsequently sero-reverted. Thus, these 'control' patients may differ from registered patients in having received a different type of blood component or number of units, in having different reasons for transfusion, or in having been transfused over a different time period. Alternatively, they may differ immunologically from the registered cases. These differences could be associated with differences in outcome, including all-cause mortality, regardless of HCV-status. As data covering most of the characteristics of the transfusion were collected during the lookback exercise, and are available to us, we shall be able to control for many of these differences. Analyses of data from single blood centres have suggested that the donor's subsequent HCV RNA status may be the strongest determinant of the recipient's test result,[19] and that recipient factors may have little effect. To aid interpretation of Register data, the above 'control' data will be supplemented with 'control' data from the general population. In this way all-cause mortality and mortality from hepatic causes can be compared with patients in the Register. This approach has been used in other natural history studies of HCV infection.[20]

We have attempted to collate a data set that is robust, reliable, and includes as many eligible transfusion recipients as possible. The process of the HCV lookback did not trace and test all recipients of potentially infected components.[5] Several factors, for example, younger age and certain specialties at the time of transfusion, have been shown to be positively associated with receiving testing. These factors are, in general, also negatively associated with being known to be dead at the time of the lookback. (Personal communication, KS) Analyses and

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interpretation of data from the Register will take account of those factors that are known to have effected the initial selection of eligible patients.

The overall response rate of 87% suggests that the registration procedures were acceptable to clinicians, and not overly burdensome. The registration forms were designed to be unambiguous, easy to complete, and short. The response rate was probably improved by our willingness to help clinicians caring for large numbers of eligible patients, to complete the forms. The registration data are also complete, only falling below 90% for those variables, like country of birth, that are not routinely recorded in patients' medical records. As such, data only appear to be missing when they are not known to clinicians, rather than because they have failed to report data that are available. Hepatitis B surface antigen (HBsAg) status was the most incompletely reported variable, being unknown for 520 of the 871 registered cases. However, 323 of these 520 patients were known to be negative for hepatitis B core antibody (anti-HBc), and further opportunities will be available to gather data on patients' HBV status at the time of annual follow-up. In contrast to reports of *past* alcohol consumption (where completeness of data approached 90%), current alcohol consumption was only available for 58% of the registered patients. However, *current* alcohol consumption was most commonly missing from the medical records of those patients who had initially reported their alcohol consumption to be nil. In these cases, *past* alcohol consumption could probably serve as a proxy for *current* alcohol consumption in any analyses of data.

Data abstracted from medical records are often inaccurate because a variety of errors can occur, either when the information is first recorded in the notes, or when it is abstracted.[21] These errors can originate with the patient, with the clinician recording the information, in a laboratory, or in the process of data abstraction.[22; 23] We could not obviate errors that

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occurred when the information was first recorded, but have made strenuous efforts to minimise the errors that can occur during data abstraction and processing. The 98% agreement between the two researchers who abstracted data at the large clinical centres was high, and compared favourably with results obtained in similar studies.[24; 25] Where errors were made, they were either random or unavoidable and unlikely to affect the integrity of the data. Entering all registration data twice should have eliminated errors in data entry.

The HCV National Register now contains anonymised data for one of the largest cohorts of individuals with 'known date' HCV infections. In the future, we plan to extend the Register to include other infections with known dates of acquisition, including prospectively ascertained perinatally acquired infections and infections where seroconversion has been documented. We hope that the Register will be used as a resource by clinicians and other researchers, that it will contribute to developing a better understanding of the natural history of hepatitis C infection, and that it will serve as a model for other chronic disease registries.

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4.0 RESULTS AND DISCUSSION

A cohort study of the natural history of hepatitis C virus during the first decade of infection

4.1 Introduction

Hepatitis C virus (HCV) is a common cause of liver disease,[1] and a major health problem worldwide.[2] Acute infection is rarely diagnosed, and information about the natural history of HCV infection has been largely accrued from retrospective studies of patients with established liver disease.[3] Such studies exclude individuals with clinically inapparent infection, and observations are often biased towards severe disease outcomes.

Opportunities for prospective studies of HCV-related disease are rare and the best known include cohorts of women exposed to contaminated immunoglobulin.[4; 5] These studies suggest that HCV-related liver disease is relatively mild,[4] but involve women who were young at the time of acquisition. As both female sex and young age are independently associated with a favourable outcome,[6] such studies may underestimate the impact of HCV-related liver disease in the wider population. Retrospective studies have attempted to determine progression from an estimated date of acquisition, based on self-reported dates of injecting drug use or from first recorded exposure to high risk blood products,[6-8] but the accuracy of these dates has been questioned.[9-11] Consequently, the rate of development of chronic liver disease and hepatocellular carcinoma remains poorly understood.

In early 1995, the UK Health Departments announced that a 'lookback' at recipients of blood transfusions prior to the introduction of anti-HCV testing, from donors subsequently found to

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be HCV infected, would be undertaken.[12] Recipients were identified from hospital records, traced and offered counselling, serological testing, and treatment for HCV infection. This process identified a large group of HCV infections with known dates of acquisition, an identifiable source, and often, no observed HCV disease progression. This study describes the HCV-related disease observed after 10 years of infection and compares the mortality from liver disease in this cohort with a group of anti-HCV negative transfusion recipients.

4.2 Methods

4.2.1.Eligible cases

At the end of 1999, 996 HCV infected transfusion recipients had been traced during the lookback.[13] For most individuals, transfusion was the only probable route of infection but eighteen were excluded because other exposure meant that their date of acquisition was uncertain (9 had injected drugs and 9 had been exposed to blood products). Fourteen cases were excluded because they could not be flagged within the NHS Central Registers (n=11) or because they were transfused after the introduction of testing of the blood supply for anti-HCV (n=3). A further 37 cases were excluded because they were HCV uninfected after full confirmatory testing, or because initial anti-HCV reactivity was not confirmed. Of the remaining 927 eligible individuals, 610 (65.8%) were known to be HCV ribonucleic acid positive, 189 (20.4%) were ribonucleic acid negative and for 128 (13.8%) the status was unknown.

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4.2.2. Controls

To provide a source of data on HCV-negative transfusion recipients, all 536 patients from the HCV lookback exercise in England who were traced, counselled, and who tested negative for anti-HCV were identified.[13] Four were excluded because they could not be flagged within the NHS Central Registers, and 57 because their dates of transfusion were unclear or because they were transfused after the introduction of anti-HCV donation testing. Of the 475 controls, 443 (93.3%) were confirmed to be HCV ribonucleic acid negative; the ribonucleic acid status of 32 (6.7%) was not known.

4.2.3. Sources of data

Data were collected from cases and controls at the time of initial counselling during the HCV lookback and from death registration. Additional data was obtained on cases at enrolment (registration) into the HCV National Register. The mechanisms of data collection, and for maximising its quality, have been described elsewhere.[13]

All-cause and liver-related mortality was compared between cases and controls. By reviewing the text of the certificate, deaths were further classified into those where HCV-related liver disease was likely to have directly caused death. This included certificates that mentioned hepatocellular carcinoma or end-stage liver disease (varices, ascites or hepatic encephalopathy) or where liver disease was coded as the underlying and only cause of death. Death certificates where liver disease or hepatitis C were mentioned as contributory factors were not included, as these were considered likely to have been influenced by knowledge of the patient's HCV status.

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evidence of past exposure to hepatitis B virus (anti-HBc positivity; P= 0.001). On average the cases were counselled six weeks earlier than the controls and have therefore been followed-up for slightly longer.

Table 1. Baseline characteristics of HCV infected and anti-HCV negative controls.

Characteristic	Eligible (927)	Controls (475)
Mean (range) years since exposure by end of 1999 †	11.1 (7.8-20.6)	11.8 (8.3-25.0)
Mean (range) age at exposure in years	43.6 (3.9-93.7)	41.5 (0.1-84.4)
Sex (%)		
Male	48.0	47.2
Female	52.0	52.8
Ethnic group (%)		
White	84.6	68.4
Non-white	5.8	7.8
Not known	9.6	23.8
Country of birth (%)		
UK	79.8	70.1
Non-UK	7.4	7.4
Not known	12.7	22.5
Alcohol consumption reported at counselling/first diagnosis (%)		
Nil	29.6	52.8
Less than 20 units/wk	45.4	38.1
At least 20 units/wk or 'alcoholism' reported	13.5	6.1
Not known	11.5	3.4
Hepatitis B status at counselling/first diagnosis (%)		
Chronic infection*	0.2	0.0
Resolved infection**	2.2	0.0
No evidence of current infection***	76.2	82.1
Evidence of past infection, but current status unknown****	2.6	1.7
Not known	18.9	16.2

* HBsAg positive; ** HBsAg negative, but anti-HBc positive;
*** HBsAg negative or anti-HBc negative; **** HBsAg unknown, but anti-HBc positive
† Excluding those who had died before the end of 1999

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4.3.1. Deaths

By the end of 1999, 120/927 (13%) of eligible cases had died, including 115/829 (14%) of the registered cases. Of the 120 deaths, 31 (26%) had mention on the death certificate of one or more liver-related conditions: hepatocellular carcinoma (n=3), liver encephalopathy (n=1), hepatic failure (n=5), cirrhosis (n=6), chronic hepatitis\hepatitis C (n=19). Of these 31 deaths only 12 were considered to have died directly *from* liver disease. These 12 cases had been infected for 9 years on average (SE: 0.72; Range: 5.6, 14.1). Eight were known to be HBsAg negative (including one anti-HBc positive), hepatitis B markers were unknown for four. Two of the 12 mentioned alcohol on their death certificate and for a further two excessive alcohol consumption was reported at counselling. Of the controls, 43/475 (9%) had died by the end of 1999 (figure 1) and only one (2%) had any liver-related condition mentioned on the death certificate. This individual died from a hepatocellular carcinoma and was known to be HCV ribonucleic acid and anti-HBc negative and was reported to consume no alcohol at counselling.

The survival analysis with all-cause mortality showed that the difference between cases and controls was only significant at the 10% level with a hazard ratio of 1.41, 95% CI (0.95 – 2.08) and P=0.08 (figure 1). Factors which significantly worsened survival were older age, being male, and level of alcohol consumption (P=0.003). Compared to drinkers of 1-20 units, survival was worse for cases with unknown (hazard ratio 2.71 (1.58-4.64)) and zero consumption (hazard ratio 1.76 (1.18-2.62)) and for those consuming ≥20 units (hazard ratio = 1.28 (0.75-2.18)). There was no evidence that the relationship between survival and age, sex, or alcohol use differed between cases and controls. There was a significant difference in

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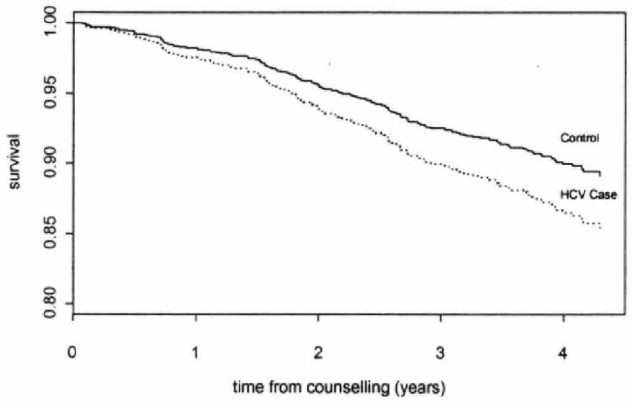
survival to death certified as *liver-related* between cases and controls (hazard ratio 12.84 (1.73 – 95.4), P=0.013). Comparison of survival to a death directly *from* liver disease (13 deaths) showed a large excess in cases but this excess was not statistically significant (hazard ratio=5.78 (0.72 – 46.7), P=0.10).

Figure 1. Survival among eligible cases and controls: Cox's proportional hazards model.



4.3.2. Liver function and disease

Data on the clinical features and laboratory investigation for liver disease were available for 829 (89%) of the eligible cases registered between February 1998 and the end of 1999. The cases that were not registered did not differ from those cases that were registered with respect to age at and time since transfusion, sex, alcohol consumption and markers of hepatitis B exposure.

Liver function, as assessed by the levels of liver transaminases in the serum (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]), was known to be abnormal in

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37% of registered cases (table 2). Liver biopsy had been performed on 362 patients, and was shown to be abnormal in 326 (90%) (table 2).

Table 2. Clinical characteristics of the 829 cases at the time of registration.

Characteristic		N	(%)
Serum liver transaminases			
Substantially elevated*		120	(14.5)
Mildly elevated**		182	(22.0)
Elevated***		5	(0.6)
Within the normal range		451	(54.4)
Not known		71	(8.6)
Physical signs or symptoms of liver disease			
Severe liver disease		34	(4.1)
Liver tumour	1		
Varices	8		
Ascites	6		
Splenomegaly	17		
Mild liver disease		81	(9.8)
No physical signs or symptoms		640	(77.2)
Not known		74	(8.9)
Liver histology†			
Biopsy taken	362		
Cirrhosis		35	(9.7)
Chronic hepatitis		270	(74.6)
Minimal change		21	(5.8)
Normal		28	(7.7)
Not known		8	(2.2)
Biopsy not performed	408		
Not known if biopsied	59		

* ALT or AST > 2x the upper limit of normal
** ALT or AST 1-2x the upper limit of normal
*** ALT or AST reported as abnormal, but degree unknown

† percentages are of those biopsied only

Some physical signs or symptoms of liver disease were reported for 115 (13.9%) of the registered cases (table 2). Twenty-one (18%) of those with features of liver disease had other reported factors that may have contributed (11 alcohol, 4 iron overload, 2 cryptogenic

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cirrhosis; 2 congenital hepatic fibrosis, 1 β-thalassaemia major, and 1 drug induced liver abscess). Single variable logistic regression was used to see which factors were associated with liver disease (mild or severe). Factors which showed some evidence of an association ($P<0.2$) were then included in a multivariable model (table 3). The factors dropped ($P>0.2$) were ethnicity, country of birth, hepatitis B status and the presence of another chronic viral infection. In the multivariable logistic regression model, HCV ribonucleic acid positivity, transfusion when older (aged over 40) and a longer time since transfusion were associated with liver disease. Sex, smoking and alcohol were not significantly associated with disease, but the direction of the effect was as in other studies.[6] The analysis was repeated comparing *severe* disease with no disease or mild disease, and HCV ribonucleic acid positivity and male sex were significant (table 3). Age transfused and time since transfusion showed similar effects as in the analysis of any disease, but were not statistically significant.

Table 3. Multivariable logistic regression analyses for signs and symptoms of liver disease

Factor	Levels	OR (mild/severe v none)	P-value	OR (severe v none/ mild)	P-value
Sex	Male	1	0.11	1	0.019
	Female	0.69 (0.44 – 1.10)		0.38 (0.17 – 0.88)	
Alcohol (units alcohol/wk)	<20	1	0.13	1	0.14
	None	1.20 (0.70 – 2.06)		1.97 (0.77 – 5.07)	
	20 or more	1.97 (1.10 – 3.51)		2.84 (1.09 – 7.41)	
	Unknown	0.93 (0.37 – 2.36)		1.19 (0.23 – 6.16)	
Age Transfused	0-19	1	0.028	1	0.24
	20-39	1.15 (0.53 – 2.51)		2.19 (0.50-9.63)	
	40-49	1.96 (0.86 – 4.53)		4.48 (1.00 – 20.1)	
	50-59	2.76 (1.27 – 6.03)		3.52 (0.79 – 15.4)	
	60+	1.38 (0.65 – 2.95)		3.22 (0.79 – 13.1)	
Time Since Transfusion	Years	1.096 (1.00 – 1.20)	0.045	1.098 (0.95 – 1.26)	0.22
HCV ribonucleic acid status	No	1	<0.001	1	0.008
	Yes	6.44(2.67 – 15.5)		4.18 (0.94 – 18.4)	
	Unknown	2.06 (0.68 – 6.18)		0.94 (0.12 – 6.95)	
Smoke	No	1	0.35	1	0.43
	Past	1.31 (0.72 – 2.39)		0.52 (0.17 – 1.58)	
	Current	1.78 (0.92 – 3.44)		0.69 (0.20 – 2.34)	
	Unknown	1.33 (0.75 – 2.35)		1.28 (0.53 – 3.10)	

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4.4 Discussion

During the first decade of infection, all-cause mortality among transfusion recipients who tested anti-HCV positive or indeterminate was 1.4-times greater than that observed in a similarly traced group of HCV-negative transfusion recipients. Although this excess mortality failed to reach statistical significance, the survival curves for the two groups were diverging, suggesting that differential mortality may increase in the future. The risk of dying *from* liver disease was almost six-fold higher amongst HCV infected individuals than negative controls, but this difference was not formally significant. Excessive alcohol consumption was implicated in at least one third of the deaths from liver disease amongst cases.

The vast majority of infected patients had no signs or symptoms of liver disease, but nearly 40% had abnormal liver function and 90% of those biopsied had abnormal liver histology. Patients who had developed physical signs or symptoms of liver disease were more likely to have been infected for longer, to be positive for HCV ribonucleic acid, and to have acquired their infections at an older age. Those with clinical features of *severe* liver disease were also more likely to be male.

This study has provided data on a group of HCV infected individuals where the time since infection is accurately known. The median time from acquisition of HCV to cirrhosis has been estimated as 30 years,[6] and so the morbidity described here is after a relatively short period of observation. Loss to follow-up has been minimised by flagging all cases and controls in the NHS central registers, and mortality data is complete. The use of death certification to establish cause of death is a potential information bias.[7; 15] Knowledge of HCV status is likely to influence content of the death certificate and this may partly explain

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the excess risk of liver-related deaths amongst cases. By examining the text of the death certificates, however, analysis was restricted to conditions likely to be clinically apparent at the time of death.

The cohort was limited to those transfusion recipients who were traceable and had survived long enough to be tested in the national lookback.[14] To reduce confounding, deaths have been compared with negative recipients also recruited by this mechanism.[13] Analysis of the lookback suggests that the HCV ribonucleic acid status of the source was the biggest influence on infection status and that recipient factors did not differ between those who tested negative and positive for HCV.[14] Information is also available on important confounding factors amongst the controls, including alcohol consumption and hepatitis B markers.

Many reported differences in the natural history of HCV reflect the stage at which cases were recruited and the length of time under observation. Studies that recruit acute infections post-transfusion[16] include individuals who resolve their infections spontaneously and those who die from other causes before developing HCV-related liver disease. In contrast, these same individuals are usually excluded from studies that recruit patients from tertiary referral centres.[3] Overall, those who have been infected for longer tend to be sicker but some individuals progress very rapidly to end-stage liver disease while others remain unaffected. This is likely to be due to individual effects, as well as other risk factors such as sex, age, and alcohol intake. Male sex is independently associated with an increased risk of progressive disease,[6] and this might explain the relatively low rate of disease observed in female cohorts.[4; 5] Acquisition of disease over 40 years of age is also associated with increased progression of fibrosis in paired liver biopsies,[6] and mathematical models estimate annual progression rates 300 times greater for men aged 61 to 70 years than for those aged 21 to 40

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years.[17] Those infected at younger ages, however, whilst initially progressing less rapidly, may progress more rapidly as they age.[18] The baseline prevalence of risk factors, such as excess alcohol use, may also explain the differential rates of progression observed in different cohorts. An excess of deaths from liver disease was only seen in two of the five cohorts studied by Seeff et al.,[16] and these were the only two cohorts not to have excluded individuals with alcoholic liver disease.

Although transfusion is a recognised risk factor for HCV transmission, transfused individuals make up a small proportion of known HCV infections in the UK.[19] As the circumstances of the transfusion may be associated with reduced life expectancy, this study may have diluted the impact of HCV on morbidity and mortality.[13] The vast majority of individuals with HCV in the UK have acquired infection by injecting drug use,[19] and may also have a shortened life expectancy due to factors other than HCV infection.[20] It has been suggested that the natural history of HCV may differ by route of infection, being less severe in those infected by injecting drug use than by transfusion.[21; 22] A cross sectional study in the UK, however, showed no evidence of difference in liver fibrosis between these two groups.[23] Cases with a history of injecting may be infected with different HCV genotypes,[23] and are likely to differ in other important ways (such as age at infection and alcohol use).

This study supports the view[4; 16; 24; 25] that HCV infection does not have a great impact on all-cause mortality in the first decade of infection. Like others,[6; 26; 27] our results suggest that the influence of alcohol is independent of other factors and is exerted only at high levels of intake. If patients can keep their alcohol consumption to a minimum, then their prognosis in the first decade of infection is likely to be improved. Continued observation of this cohort

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will determine the outcome of HCV infection in the longer-term and enable us to evaluate the impact of anti-viral treatment.

4.5 References

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5.0 REGISTER OUTPUTS

5.1. Published papers and abstracts

- Harris HE, Ramsay ME, Andrews N, Eldridge KP on behalf of the HCV National Register Steering Group. A cohort study of the natural history of hepatitis C virus during the first decade of infection. *British Medical Journal* in press.

- Harris HE, Ramsay ME, Heptonstall J, Soldan K, Eldridge KP. The HCV National Register: towards informing the natural history of hepatitis C infection in the UK. *Journal of Viral Hepatitis* 2000; **7**: 420-427.

- Harris HE, Ramsay ME, Eldridge KP. Signs and symptoms of liver disease after 10 years of infection with heptaitis C virus. Data from a national cohort of patients who acquired their infections on a known date. *Journal of Hepatology* 2000; **32**: (Supp 2) 98.

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5.2. Presentations

- Harris HE. 'The HCV National Register: A register of HCV infections with known dates of acquisition.' Presented at the MAINLINERS' 5th International Conference on Hepatitis C, Amsterdam, 2000.

- Harris HE, Ramsay ME, Eldridge KP. 'Signs and symptoms of liver disease after 10 years of infection with hepatitis C virus. Data from a national cohort of patients who acquired their infections on a known date.' Presented at the Public Health Laboratory's Annual Scientific Meeting, Warwick, September 2000.

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- Harris HE, Ramsay ME, Eldridge KP. 'Signs and symptoms of liver disease after 10 years of infection with hepatitis C virus. Data from a national cohort of patients who acquired their infections on a known date.' Presented at the European Association for the Study of the Liver's Annual Scientific Meeting, Rotterdam, Netherlands, May 2000.

- Harris HE, Ramsay ME. 'The clinical course of HCV-related disease in the first decade of infection: A preliminary analysis of data from the HCV national register.' Presented at the American Association for the Study of Liver Disease's Annual Scientific Meeting, Dallas, Texas, November 1999.

- Harris HE, Ramsay ME, Robinson EAE. 'The clinical course of HCV-related disease in the first decade of infection: A preliminary analysis of data from the HCV national register.' Presented at the British Blood Transfusion Society's Annual Scientific Meeting, Edinburgh, September 1999.

- Harris HE, Ramsay ME. 'The clinical course of HCV-related disease in the first decade of infection: A preliminary analysis of data from the HCV national register.' Presented at the British Association for the Study of the Liver's Annual Meeting, Hammersmith Hospital, London, September 1999.

- Harris HE, Ramsay ME. 'The clinical course of HCV-related disease in the first decade of infection: A preliminary analysis of data from the HCV national register.' Presented at the 24th PHLS Annual Scientific Conference, Warwick, September 1999

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- Harris HE, Ramsay ME, Robinson EAE. 'The HCV national register.' Presented at the British Blood Transfusion Society's Annual Scientific Meeting, East Midlands Conference Centre, Nottingham, September 1998.

- Harris HE, Ramsay ME, Robinson EAE. 'A national register of HCV infections.' Presented at the British Association for the Study of the Liver's Annual Meeting, John Radcliffe Hospital, Oxford, September 1998.

Two presentations describing (i) the HCV national register and the data contained therein (section 3.0 of this report) and (ii) the natural history of HCV during the first decade of infection (section 4.0 of this report), are included in the appendices to this report (section 6.0).

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6.0 APPENDICES

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