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executive summary

Sixty thousand people in the UK will progress towards serious liver disease this year, approximately 460 will have a liver transplant and at least 1600 will die from liver cirrhosis as a consequence of hepatitis C (HCV) infection, an infection that we have the ability to identify and treat[1]. However, much of the infection remains hidden, either undiagnosed or in disenfranchised social groups, with up to 400 000 people with HCV infection remaining undiagnosed[2]. This will remain the case with tragic consequences unless urgent action is taken by the Government to remedy deficiencies in the ability of the NHS to respond to the HCV epidemic. In other words, HCV is the 'Public Stealth Disease'.

This may sound alarmist but the harsh reality is that HCV infection is a serious public health problem that the UK is not equipped to address. US projections[3] suggest that by 2008, for example, the number of patients requiring liver transplants because of HCV will increase by 528 per cent. The number of cases of hepatocellular carcinoma and cirrhosis will also increase and it is unlikely that the UK will be far behind. The costs of liver transplants alone would be £123 million in the UK based on these projections. So unless the Government begins planning for this increase now by commissioning services and increasing funding, our existing services will be overwhelmed and many more people will progress to end stage liver disease and die.

Until recently, there seemed little political will to implement the necessary changes and continuous juggling of priorities has meant that HCV infection has continually lost out to other more 'high profile' health issues. Few commissioning bodies have implemented strategic action to improve HCV management, identify people infected and educate healthcare professionals. To make matters worse, guidelines, including those from the National Institute for Clinical Excellence (NICE), discourage treatment of some members of the largest group of infected people - injecting drug users. Where a positive approach to treatment is advocated, as in NICE's guidance issued in 2000 where widespread use of combination treatment for all eligible patients was recommended, it has little impact due to insufficient funding. We still only treat 10% of the number of patients treated in France and Germany[4]

Now there is evidence of a change in attitudes among government and we have a new injection of funds courtesy of the increased spending programme on the NHS announced by the Chancellor of the Exchequer in April 2002. In addition, we have a growing number of new treatments giving clinicians an unprecedented opportunity to alter the natural history of a disease that is responsible for escalating healthcare costs as patients progress towards end stage liver disease.

However, it is not all about treatment. A recent survey of public attitudes to hepatitis C, commissioned for this report, has shown that more could be done to educate the public about HCV infection, how it is transmitted and its serious consequences[5]. We also need to create greater awareness of HCV infection and destigmatise the disease amongst at-risk populations so that more come forward for testing and treatment. As we move towards a UK wide strategy on prevention, care and treatment against the HCV epidemic and look to reduce the future impact on public health, the following elements need to be considered:

- **an accurate picture of the incidence and prevalence of hepatitis C in the UK is needed to aid planning and delivery of effective healthcare services**
- **a public information campaign is needed to raise awareness of hepatitis C across the whole population and, most importantly, in high risk groups**
- **diagnosis of HCV infection needs to be more accessible to maximise numbers coming forward**
- **we have to acknowledge the support of the public for removal of the discrimination against injecting drug users in the UK[5] and call for a review of clinical guidelines and NICE guidance to enable treatment of those users in rehabilitation**
- **new treatment approaches should be appraised now to ensure the UK is in step with new international standards of care**

This report reviews the epidemiological evidence, summarises what an 'ideal specialist service should comprise and highlights the economic toll imposed by HCV. It considers some of the issues facing clinicians, purchasers and providers in attempting to create greater awareness of this disease. Most importantly, it highlights the importance of working together to create an accessible and comprehensive system for the diagnosis and management of HCV infection and that it is done now. We hope that this report will articulate this urgent need for action by health professionals and other agencies and raise HCV up the public health agenda.

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introduction

Over the last few years, microbiologists, public health doctors, infectious disease specialists and hepatologists increasingly recognised that HCV, an infectious blood-borne virus, causes considerable morbidity and mortality in the UK. Increasing numbers of people are being diagnosed with HCV and a larger proportion of infected people are presenting for treatment, driven by greater awareness of the condition among healthcare professionals and the lay public, as well as the increasing number of effective new treatments. However, many remain undiagnosed as serious symptoms can take 25 years to emerge.

Despite this, HCV rarely attracts the attention of the medical and lay media, or purchasers and providers, to the same extent as, for example, HIV, Parkinson's disease or cervical cancer. Yet, HCV is more common than HIV even among some high-risk groups. Moreover, the Chief Medical Officer noted in his 2001 annual report[1] that, during 2000, liver cirrhosis killed more men than Parkinson's disease and more women than cervical cancer. HCV accounts for 40 per cent of the cases of end-stage cirrhosis[2].

Against this background, the British Liver Trust aims to raise awareness of this devastating disease and improve management for HCV-positive people. As part of this on-going campaign, this document aims to educate commissioners in primary and secondary care about the disease. The report reviews the epidemiological evidence - to facilitate health needs assessments - outlines elements of a specialist service and highlights the economic toll imposed by HCV. We hope that the report will help decision-makers both nationally and locally to quantify and analyse the health and economic burden imposed by HCV across the UK. We also hope that the report might help hepatologists and infectious disease specialists develop a business case with their local trusts.

The focus on HCV is timely. Improving HCV care fits within the medico-political context developed in the National Service Framework (NSF) for Cancer as well as, in a broader context, the Modernisation Agenda. Indeed, the Government is due to publish its national HCV strategy shortly, which will provide a framework to manage the disease and set priorities. This forms part of a broader campaign by the Department of Health and other organisations, which are developing several strategies to reduce the risk of HCV and the likelihood of progression to chronic liver disease:

- The HCV strategy.

- Guidance by the National Institute for Clinical Excellence (NICE) recommending the use of combination treatment with ribavirin and interferon alpha for certain patients with HCV.

- Clinical guidelines on HCV management published by the British Society of Gastroenterology (BSG) and the Royal College of Physicians. The guidelines cover diagnosis, counselling regarding transmission, and treatment.

- Guidance on HCV for those working with drug users from the Department of Health.

These elements need to be forged into a framework that the Chief Medical Officer calls 'an integrated approach ... for hepatitis C which brings together prevention, control and treatment'. This also contributes to the Government's objective of developing a 'concerted and co-ordinated' strategy to reduce the trend towards higher levels of chronic liver disease and cirrhosis.

Against this background, the report considers some of the issues facing clinicians, purchasers and providers attempting to implement this 'concerted and co-ordinated' strategy. This document also aims to support the British Liver Trust in its calls for a national strategy for chronic liver disease, possibly leading to a National Service Framework. As the number of relatively expensive - although cost-effective - treatments for HCV increases, the implementation of better, co-ordinated services for patients suffering from chronic liver disease is set to become an important priority for all commissioners. As one paper[3] examining the epidemiology of HCV in the UK concluded recently, there is a 'need for an urgent appraisal of service provision and a review of prevention and treatment strategies' against blood borne infections.

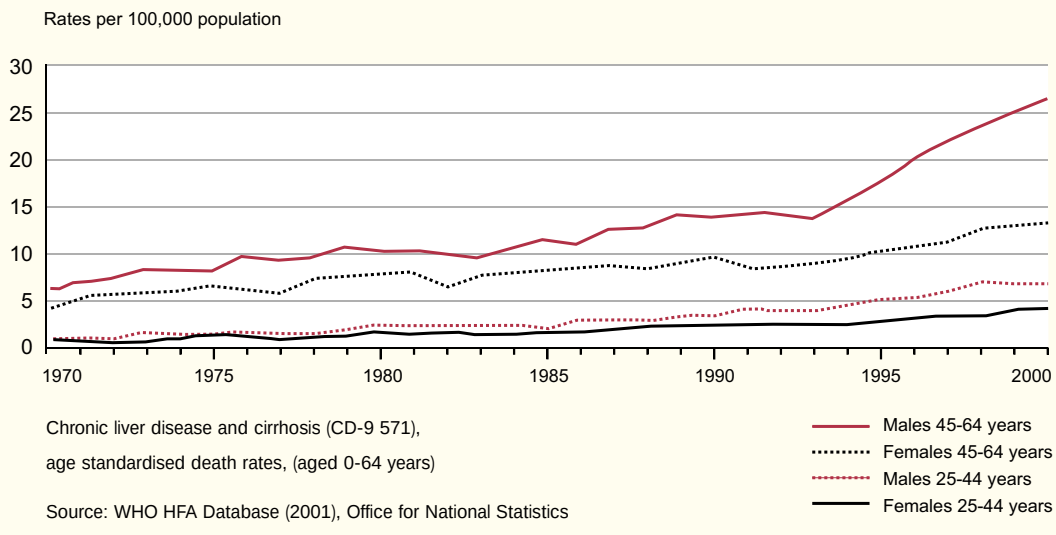
the burden imposed by chirrhosis and chronic liver damage

To set the scene for our discussion of HCV, we will briefly consider the burden imposed by cirrhosis and chronic liver disease generally. Cirrhosis, which arises from prolonged liver damage, represents an important cause of morbidity and mortality, the Chief Medical Officer noted in his 2001 annual report. For example, cirrhosis killed more than 4000 people in the year 2000 in England. Two-thirds of these patients are younger than 65 years of age[1].

Moreover, the UK is currently experiencing a marked increase in deaths from chronic liver disease and cirrhosis (see figure 1). For example, the Department of Health estimates that since the early 1970s[1]:

- among people aged between 45 and 54 years, the death rate from chronic liver disease and cirrhosis increased more than four-fold among men and three-fold in women.
- in men and women aged between 35 and 44 years, the increase in the death rate from chronic liver disease and cirrhosis is even more marked: eight-fold and almost seven-fold respectively.
- in those aged between 25 and 34 years, the death rate from chronic liver disease and cirrhosis increased four-fold.

Figure 1: Rising trend in deaths from chronic liver disease



Chronic liver disease and cirrhosis (CD-9 571),
age standardised death rates, (aged 0-64 years)

Source: WHO HFA Database (2001), Office for National Statistics

- hospital admissions for chronic liver disease and cirrhosis doubled between 1970 and the mid-1980s. Today, admissions for chronic liver disease and cirrhosis continue to rise steadily. In 1999, approximately 9000 and 3000 hospital admissions were for main diagnoses of alcoholic liver disease and liver cirrhosis respectively.

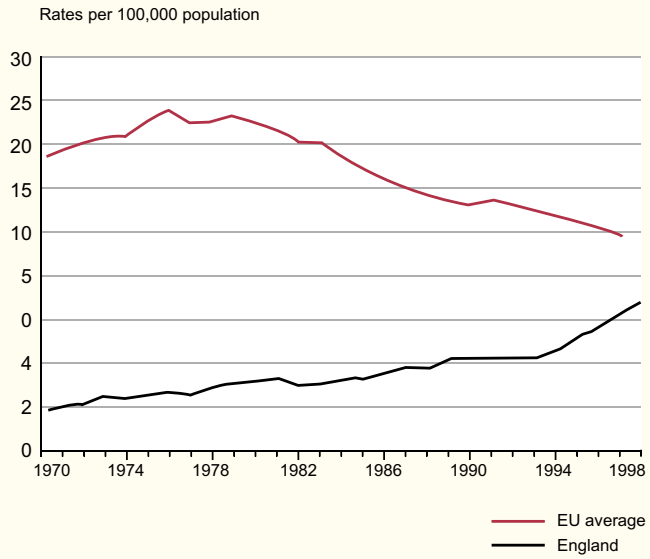
- the NHS Hospital Episode Statistics for 1999/2000 and 2000/2001 stratified by primary diagnosis (see table 1) shows that the approximately 5000 episodes of viral hepatitis in England annually account for almost 14 thousand bed days a year. Most patients suffering from viral hepatitis are in the prime of life and their average age is considerably younger than those suffering from liver disease as a whole. Moreover, patients with viral hepatitis are more likely to be male and are more likely to be admitted to hospital than those with liver disease more generally.

Table 1: The NHS Hospital Episode Statistics for primary diagnoses of viral hepatitis and liver disease during 1999/2000 and 2000/2001

Statistic	1999/2000		2000/2001	
	Viral hepatitis	Liver disease	Viral hepatitis	Liver disease
Finished episodes	4932	26,726	5193	27,827
Proportion of episodes admitted (%)	90	73	89	71
Proportion Male (%)	67	59	65	58
Proportion Emergency admissions (%)	30	59	28	61
Proportion elective admission from waiting list (%)	53	26	46	25
Mean waiting time (days)	46	32	53	34
Median waiting time (days)	31	16	34	17
Mean length of stay (days)	4.3	11.6	5	12.4
Median length of stay (days)	1.0	7	2	7
Mean age (years)	40	53	41	53
Proportion aged 15-59 years (per cent)	83	65	84	65
Proportion aged 75+ years (per cent)	2	8	2	8
Proportion day case (per cent)	26	11	36	12
Bed days	13,658	196,645	13,962	210,205

Indeed, the rising death rate from cirrhosis is in marked contrast to other countries in the European Union (see figure 2). Traditionally, death rates from cirrhosis are higher in continental European countries than the UK. In 1970, for instance, the death rate for liver cirrhosis in England was around seven times lower than the European Union average. However, while mortality from cirrhosis is stable or falling in continental Europe, death rates are rising in the UK[1].

Figure 2: Narrowing gap between England and European Union average death rates from chronic liver disease



Chronic liver disease and cirrhosis (CD-9 571), age standardised death rates, (aged 0-64 years)

Source: WHO HFA Database (2001), Office for National Statistics

Several factors contribute to the rise in deaths from liver disease. However, changes in the British lifestyle seem to underlie most of the increase in liver cirrhosis. While liver cirrhosis can arise as an inherited disease, from parasitic infections or as a side effect of some drugs, alcohol misuse remains the leading cause of prolonged liver damage. Indeed, the rise in deaths from cirrhosis, parallels the marked increase in total alcohol consumption during the early 1970s. On average, adults consumed 6 litres of pure alcohol each in 1969. This rose to 9.5 litres in 1976, a level of consumption that remained relatively stable over the next 25 years[1].

As cirrhosis often takes several years to emerge, the NHS is now managing the consequences of the rise in alcohol consumption. As the Chief Medical Officer noted in his 2001 annual report: "Although we cannot be completely certain, by far the most convincing explanation for the increase in death rates from chronic liver disease and liver cirrhosis reported [in the UK] is higher levels of alcohol consumption". However, the report adds that patterns of increased drinking at earlier ages are beginning to have serious public health implications. During 2000, cirrhosis killed around 500 men and almost 300 women aged between 25 and 44 years. Moreover, differences in alcohol consumption seem to underlie the variations in the risk of liver disease among social and occupational groups[1].

However, excessive alcohol consumption is not the sole factor contributing to the rise in cirrhosis. Viral hepatitis - in particular HCV, the focus of this report - represents another important cause of chronic liver disease. Moreover, HCV and alcohol abuse can interact: alcohol increases the rate at which viral hepatitis progresses.

HCV: an introduction

During the 1940s, microbiologists began to divide hepatitis into two types: infectious and serum. However, in the 1970s, researchers found cases of multiple attacks of hepatitis in people addicted to narcotics that fitted into neither of these types. Therefore, a new disease was born: non-A, non-B (NANB) hepatitis. Over the next few years, researchers began to recognise that NANB hepatitis posed a considerable public health problem. By the late 1970s, for example, between 7 and 10 per cent of people who received blood transfusions developed hepatitis. In 90 per cent of these cases, NANB hepatitis seemed responsible[4].

We now know that several viruses are responsible for NANB hepatitis (see table 2), including HCV. The specific disease now recognised as HCV infection emerged during the 1970s. Ironically, however, researchers dismissed the condition as a benign change in liver enzymes following blood transfusions. HCV was not cloned until 1989[5]. Since then, a growing and compelling body of evidence emerged suggesting that HCV causes considerable morbidity and a markedly increased risk of mortality. Moreover, HCV seems to be a relatively common cause of viral hepatitis. For example, a study[6] from researchers at Ninewells Hospital, Dundee, found that of 4992 patients infected with viral hepatitis in Tayside between 1989 and 1999, 469 (9.4 per cent) were HCV positive. In comparison, 86 (1.7 per cent) and 187 (3.7 per cent) were positive for hepatitis A and B (HBV) respectively.

Table 2: The subtypes and characteristics of viral hepatitis

Characteristic	A	B	C	D	E	G
Course	Acute	Chronic	Chronic	Chronic	Acute	Not clear
Discovered	1973	1965	1989	1977	1990	1996
Infection Route	Oral	Body fluids; sex; blood-to-blood	Blood-to-blood	Blood-to-blood; in conjunction with Hep B	Oral	Blood-to-blood; possibly sex
Vaccine	Yes	Yes	No	Indirect immunity from Hep B vaccine	No	No
Long-term prognosis	Lasts up to 6 months	Carrier; cirrhosis; liver cancer	Carrier; cirrhosis; liver cancer	May exacerbate Hep B	None known	None known

hepatitis C as a cause of liver disease

HCV is especially likely to lead to chronic liver disease. Indeed, in the industrialised world, HCV accounts for[2]:

- 40 per cent of cases of end stage cirrhosis.
- 60 per cent of cases of hepatocellular carcinoma.
- 30 per cent of liver transplants.

However, chronic HCV tends to be insidious. (We discuss the morbidity and mortality associated with HCV in more detail below.) Indeed, many infected people may never develop chronic or acute symptoms. On the other hand, in around a fifth of patients, chronic HCV leads to cirrhosis, usually 20 or 30 years following the infection.

Chronically infected patients show active HCV in their blood - which can be measured by quantifying the amount of viral RNA (the "viral load"). As a result, viral load offers a valuable way to measure the effectiveness of treatment. Nevertheless, screening based on viral load may offer different results from the antibody tests used in many papers. Antibody tests indicate previous HCV exposure rather than active infection. Nevertheless, among injecting drug users, around three-quarters of those who express HCV antibodies are also positive for HCV-RNA. These "carriers" can transmit the infection[7] through four transmission routes[7]:

- Unscreened blood.
- Injecting drugs.
- Mother-to-child.
- Sexually (infrequently).

As mentioned below, injecting drug use accounts for most cases of HCV presenting to the NHS. The disenfranchisement of injecting drug users from mainstream health services as well as their disengagement from society more widely is another important reason why HCV remains the public stealth disease. Indeed, a systematic review[8] of the global literature concerning HCV epidemiology suggested that there is no "recognisable" transmission factor or route in up to half the cases. However, Rosenberg[9] notes that most hepatologists and nurses find that on "close questioning in private" most cases without a recognisable route of transmission at first sight, directly or indirectly relate to injecting drug use.

new HCV treatments drive sea change in attitudes

Over recent years, clinician's attitudes towards HCV management have undergone something of a sea change. Until recently, clinicians could offer people with HCV little more than symptomatic management. However, a growing number of treatments - currently one of two types of interferon either alone, in combination with other agents, or pegylated - offer the opportunity to alter the natural history of HCV, potentially reducing morbidity and mortality.

A comprehensive review of the clinical literature is outside the scope of this report. However, because of the limited efficacy seen in many studies of interferon alfa, combination therapy (interferon alfa and ribavirin) is recognised as the treatment of choice for people suffering from chronic HCV. Indeed, both NICE and the former Scottish Health Purchasing Information Centre (SHPIC) recommended combination therapy for interferon-naive patients and relapsed patients (see below).

A recent *Health Technology Assessment* review[10] examined 19 randomised controlled trials and two meta-analyses assessing combination therapy in chronic HCV. The authors concluded that over 24 weeks, 33 per cent of patients treated with combination therapy showed sustained responses measured by viral load. This compared with 6 per cent of those managed with interferon alfa alone. Over 48 weeks, the proportions were 41 and 16 per cent respectively. Among patients who relapsed following interferon alfa, 24 weeks combination treatment produced sustained viral load responses in 49 per cent of patients. In contrast, just 5 per cent of relapsed patients responded to interferon alfa alone.

Moreover, emerging evidence suggests that the viral load responses translate into long-term benefits on cirrhosis and hepatocellular carcinoma. For instance, Japanese researchers[11] treated 90 patients suffering from chronic HCV with either symptomatic management or interferon alfa three times a week for 24 weeks. Mean follow ups were 8.2 and 9.2 years respectively. Only a small proportion of patients showed a sustained response to interferon alfa. Nevertheless, interferon alfa prevented a decline in compensated cirrhosis as well as inhibiting the development of hepatocellular carcinoma compared to symptomatic treatment. This study suggests that interferon potentially reduces the likelihood of the late complications associated with HCV.

Currently, we lack long-term studies assessing the impact of combination therapy on the risk of developing cirrhosis and hepatocellular carcinoma. However, it seems reasonable to suppose that the effect will be at least as marked as with interferon alfa alone.

Despite these promising results, current treatments have limitations. For example, there are several genetic variants of HCV. The PHLS Central Public Health Laboratory found that HCV type 3a (genotype 3, subtype a) was the commonest genotype in antenatal clinic attendees in London as well as in the Northern and Yorkshire region[12].

Characterising the HCV genotype is important as it can influence outcome. For instance, genotype 1 seems to be associated with a poorer treatment response than some other genotypes[13]. So new therapies are needed that show greater efficacy against less responsive genotypes.

Moreover, resistance to antiviral drugs used to manage HCV can emerge and, after an initial decline in viral load, levels rise again. In common with HIV, a combination of high risk of mutation and a fast replication rate leads to the emergence of a plethora of HCV 'quasispecies'. The genomes of HCV genotypes vary by between 31 and 35 per cent. In contrast, quasispecies' genomes differ by just 1 to 9 per cent14. Nevertheless, the clinical consequences can be marked. In some cases, the quasispecies allow the HCV to evade the immune system - which might be one reason why most people do not clear the initial acute infection. In other cases, the viral quasispecies are resistant to antiviral medication[15].

Moreover, side effects can pose a problem, especially as treatment needs to be protracted. For example, around 20 per cent of patients taking combination therapy discontinue before he end of 48 weeks for a variety of side effects, including insomnia, depression, irritability and anaemia[13]. The combination of less than total efficacy, resistance, non-responsive genotypes and poor tolerability in a significant minority of patients drove the search for alternative antiviral drugs. For example, the changed pharmacokinetics (the way the body absorbs, metabolises, distributes and excretes a drug) of pegylated interferon suggests that it is superior to conventional interferon alfa.

Pegylation, which adds straight chain polyethylene glycol groups (PEG) moieties to the protein, in a 1:1 molar ratio, is a well-established protein modification technique and results in delayed renal clearance and an extended plasma half-life from approximately 4 hours to 40 hours. The fact that pegylated proteins remain in the circulation for longer led to the hypothesis that the efficacy of pegylated interferon could be enhanced due to more sustained therapeutic pressure on the virus. Indeed, pegylation has allowed once-weekly dosing and seems to enhance interferon's antiviral effects[13].

More recently, interferon has been substituted with pegylated interferon in combination with ribavirin in an attempt to improve both the sustained virological response [(SVR) defined as an undetectable level of HCV RNA (<100 copies per ml)] and the treatment response of the genetic variants of HCV16. In patients with chronic HCV infection, once weekly peginterferon alfa-2b was more effective than interferon alfa-2b given three times weekly[17]. In a study of 1530 patients with chronic HCV, peginterferon alfa-2b (1.5µg/kg) once weekly plus ribavirin (weight-based dose) given for 48 weeks significantly increased the SVR rate (61 per cent) when compared with standard interferon alfa-2b plus ribavirin (SVR rate 47 per cent) for the same duration[18]. The benefit was most apparent in patients with genotype 1 infection but response rates for patients with genotype 2 and 3 were similar and uniformly high[19]. A combination of peginterferon alfa-2b and ribavirin received a licence in March 2001.

Given the increasing evidence for new approaches to treatment involving effective pharmacological innovation and the lurking epidemic, discussed in the next section, HCV is set to rise up the healthcare agenda.

the epidemiology of HCV

HCV poses a public health problem worldwide, especially as the rapid evolution of genotypes and quasispecies hinders attempts to develop a vaccine. According to the World Health Organisation, around 3 per cent of the world's population is infected with HCV[9]. HCV prevalence tends to be higher in the middle and Far East than in the West[8]. For example, in Egypt approximately 24 per cent of the population may carry HCV[18]. As a result, the authors of a systematic review of the global literature argued that HCV represents "an important public health issue" worldwide and called for public health officials to develop strategies to inform and educate the public about HCV[8].
The British Liver Trust believes that we should heed this call in the UK.

Indeed, HCV is the commonest infective cause of chronic liver disease in Europe. In a recent literature analysis[19], the HENCORE (Hepatitis C European Network for Co-operative Research) collaboration reported that, on average, 1 per cent of blood donors in the European Union were HCV positive. Moreover, the review suggested that the prevalence of HCV among haemodialysis patients and injecting drug users was between 20 to 30 per cent and approximately 80 per cent respectively. However, HCV prevalence was markedly higher in southern Europe compared to the northern countries. The north-south gradient was 0.04 to 2 per cent. Nevertheless, the increasing travel around Europe and worldwide offers plenty of opportunity for HCV transmission.

In the UK, the Department of Health estimate that around 250 000 people in England are infected with HCV. For example, assessing the prevalence of HCV in antenatal clinic attendees offers an indication of the burden of illness in the general population. Researchers based at the PHLS Central Public Health Laboratory used samples collected for the routine testing for rubella immunity to assess HCV prevalence in antenatal clinic attendees in London as well as in the Northern and Yorkshire region. The adjusted overall prevalence of antibodies against HCV was 0.43 per cent among women attending antenatal clinics in London. This compared to 0.21 per cent in the Northern and Yorkshire region. The authors comment that the low prevalence is "consistent" with that arising from injecting drug use[11] These figures should allow purchasers and providers to estimate best and worse cases for the prevalence in the local area.

However, as the next section shows, there is no room for complacency. The number of people infected with HCV rose markedly since the 1960s and 1970s. As a result, the burden of illness imposed by HCV should also increase markedly over the next five to 10 years[1]. A response to a question (13 November 2000) in the Houses of Parliament underscores the marked increase in the number of laboratory reports of HCV in recent years. According to the Parliamentary answer, the number of laboratory reports of HCV increased more than 2.5 fold between 1995 and 1999 (see table 3).

Table 3: Number of laboratory reports of HCV

Year	England and Wales	Scotland	Northern Ireland	Total
1995	1667	1125	58	2850
1996	2544	1236	29	3809
1997	3058	1494	26	4578
1998	4488	2052	38	6578
1999	5561	2009	23	7593

injecting drug users and impact of harm reduction strategies

"Although transmission of HIV infection through injecting drug use is low, transmission of hepatitis B and hepatitis C infections remains a major concern."

This conclusion, from the 2000 annual report of the Unlinked Anonymous Prevalence Monitoring Programme (UAPMP), underscores the central importance of targeting injecting drug users in strategies to reduce the morbidity and mortality arising from viral hepatitis. UAPMP monitors rates of HBV and HCV infection among injecting drug users attending specialist treatment centres and support agencies. A third of injecting drug users attending these services expressed HCV antibodies. However, overall only 40 per cent of those expressing antibodies were aware that they were HCV positive. Moreover, HCV transmission is an ongoing problem among injecting drug users, despite educational and other strategies to reduce sharing of injecting paraphernalia. The UAPMP's findings underscore the continuing risk: one in 12 of those who started injecting drugs over the last three years were HCV-positive[20]. We will return to this issue later.

The UAPMP showed several variations in prevalence and attitudes across the UK. The prevalence of HCV among people injecting drugs was highest in London and the North West. However, 58 per cent of HCV-positive people in London were aware of their infection compared to 35 per cent in the rest of England and Wales[20]. Such regional differences underscore the importance of a co-ordinated national strategy to reduce 'postcode' variations in management and outcome.

On the other hand, there is little doubt that needle and syringe exchange programmes combined with other strategies have made some inroads into the relatively high prevalence of HCV among injecting drug users. After increasing for several years, the UAPMP found that the rate of direct sharing of injecting equipment has now levelled off[20]. As a result, HCV prevalence among people injecting drugs shows signs of beginning to decline.

In Edinburgh, for example, antibody testing suggested that HCV prevalence among those less than 25 years of age declined from 69 per cent in 1989/90 to 13 per cent in 1997. Among those aged at least 25 years, HCV declined from 80 per cent in 1989/90 to 54 per cent in 1997[21].

Meanwhile, in Glasgow, the prevalence among injecting drug users aged less than 25 years of age declined from 91 per cent in 1990 to 43 per cent in 1997. The prevalence among older addicts did not decrease significantly[21]. Presumably, many of the older addicts began their injecting careers before the needle and syringe exchange programmes and educational strategies.

Nevertheless, between 1995 and 1997, 17 per cent of injecting drug users aged between 15 and 19 years in Edinburgh and Glasgow were HCV-positive. Therefore, needle and syringe exchange as well as other interventions have not eliminated HCV among young people who inject drugs of abuse. As a result, the authors concluded that more investigations and new approaches to prevention are needed to further reduce the burden of illness among injecting drug users[21].

Other studies confirm that HCV continues to pose a considerable problem among injecting drug users despite strategies to prevent transmission of blood borne infections. This obviously represents a reservoir of infection that could potentially cross over to the wider population. Three studies exemplify both the current burden of HCV among injecting drug users as well as the on-going risk of transmission.

Firstly, researchers[22] from the Scottish Centre for Infection and Environmental Health, Glasgow, determined the incidence of HCV in 212 injecting drug users who underwent at least two voluntary HIV tests between 1993 and 1998. Of these, 77 per cent showed detectable HCV antibody in their first specimen. Twenty-five per cent of those who did not show HCV in the first sample showed antibodies (seroconverted) by the time clinicians took the second sample. This suggests an incidence of HCV among injecting drug users of 28.4 per 100 person-years. However, incidence was highest among older men. Again, this presumably reflects the longer history of injecting drug use.

Secondly, McIntyre and colleagues[23] estimated the prevalence of HCV, HIV and human T-cell leukemia/lymphoma viruses (HTLV) type 1 and 2 among injecting drug users in Tayside between 1993 and 1997 (see table 4). Overall, 65.3 per cent of injecting drug users was HCV positive on antibody testing. HIV and HCV antibodies were most common among injecting drug users aged over 25 years. HCV prevalence fell only in younger, female injecting drug users between 1993 and 1997.

Table 4: The prevalence of blood-borne viruses in injecting drug users in Tayside 1993-7

Virus	Number tested	Number positive	Percentage positive
HIV	802	29	3.6
HCV	691	451	65.3
HTLV	679	0	0

The high incidence among older men found by Roy[22] is reflected in reports of the PHLS Communicable Disease Surveillance Centre where, of a total number of laboratory reports of HCV infection in men in England and Wales in 1999 (3785), 65 per cent were in the 25-44 age group.

Finally, in England and Wales, a study by Hope and colleagues[23] found that 30 per cent of 2203 injecting drug users enrolled through agencies and 758 recruited from the community were HCV positive. This compares to 21 and 0.9 per cent for HBV and HIV respectively. Several factors emerged as significantly increasing the likelihood of being HCV positive (see table 5). However, the authors commented that the prevalence of HCV is lower in England and Wales, which implemented “comprehensive” programmes aimed at harm reduction, than in other industrialised nations. Again, this suggests that harm reduction programmes can make a difference, but are insufficient alone to manage the public health problem posed by HCV.

Table 5: Factors associated with an increased risk of HCV infection

Longer injecting careers
Older age
Residing in London
Recruited through drug agencies
Testing positive for HBV
Previous voluntary HIV tests

Moreover, HCV among injecting drug addicts is not solely a problem confined to inner cities. Researchers[24] from St George's Hospital Medical School, London, screened 78 male and 24 female adults undergoing treatment for drug use who lived in a mixed urban-rural area in southeast England for blood borne viruses. The authors found that "the prevalence of HIV, HBV and HCV in the rural population is as high as has been reported for inner cities".

Indeed, more than half of the drug users screened were HCV positive (see table 6). The proportions that were HCV positive were similar between sexes, whether the person lived in towns or villages and according to sexual risk behaviour. On the other hand, age at interview, age the person started using opioids and duration of opioid use were associated with the risk of being HCV positive. The authors concluded by highlighting "the need for an urgent appraisal of service provision and a review of prevention and treatment strategies" against blood borne infections.

Table 6: Results of testing for antibodies against HIV, HBV and HCV among drug users living in southeast England

Group	Number tested	Number positive	Percentage positive
HIV-1	27	1	3.7
HBV	88	18	20.4
HCV	86	48	55.8

prisons

Many injecting drug users spend time in prison. Indeed, according to UAPMP, over half of injecting drug users had been in either prison or a young offenders' institution. UAPMP also found that people who spent time in custodial sentences are especially likely to be HCV positive. Thirty-eight per cent of injecting drug users who had been in prison were HCV positive. This compared to 24 per cent of those who had not[20].

Similarly, Weild and colleagues[25] studied the prevalence of and risk factors for transmission of blood borne viruses in eight prisons. Seven per cent of prisoners were positive for HCV, compared to 0.4 and 8 per cent for HIV and HBV respectively. Moreover, 24 per cent reported injecting drugs at sometime during their lives and 30 per cent of these injected drugs while in prison - equivalent to six per cent of the total prison population. Three-quarters of the those who injected while in prison shared needles or syringes. Among adults injecting drugs while in prison, 31 per cent were positive for HCV, compared to 0.5 and 20 per cent for HIV and HBV respectively. Although Weild only studied a small segment of the prison population, these findings suggest that any comprehensive strategy that aims to reduce the morbidity and mortality arising from HCV needs to recognise and manage the problem of drug abuse in prisons.

genitourinary clinic attendees

Sexual intercourse offers another route for HCV transmission, which is especially important given the number of drug abusers who fund their addiction through prostitution. However, the risk of HCV infection from sexual intercourse appears to be low with estimates of less than 5 per cent of the regular partners of those infected with HCV also becoming infected[1], but clinical studies on this transmission route have produced mixed results. This is in part due to the nature of the population being studied and whether other routes of infection can be completely ruled out.

Zylberberg and colleagues[26] performed extensive epidemiological and virological analysis in 24 couples in which both partners were anti-HCV positive. Of all the 48 spouses, 33 had a major risk factor for HCV transmission (injecting drug use or blood transfusion) and 11 of the 12 couples with the same genetic type of HCV infection had at least one of these major risk factors in both spouses.

In his review article, Rosenberg[27], highlights studies that have found the risk to be between 0 and 27 per cent. However, these studies have been conducted in widely differing groups of subjects. However, clearer evidence has arisen from studies of couples where one partner was infected with HCV via a blood product. The low rate of transmission (between 1 and 3 per cent) found in these couples, in which other risk factors are rare, does suggest that sexual transmission is likely to be infrequent.

Goldberg and colleagues[28] analysed residual syphilis serology specimens obtained from genitourinary clinics in Glasgow, Edinburgh and Aberdeen during 1996/97. In general, the prevalence of HCV among heterosexual men and women as well as homosexual or bisexual males (none were injecting drug users) ranged from 0 and 1.2 per cent. However, the prevalence reached 7.7 per cent among the 52 homosexual or bisexual males in Aberdeen. Table 7 summarises the results. Three females among the HCV positive people who did not inject drugs were not UK nationals or had lived abroad. None of the HCV positive men were not UK nationals or had lived abroad.

Table 7: HCV prevalence among heterosexuals, homosexual/bisexual not injecting drugs as well as injecting drug users in Scotland

Group	Number tested	Number positive	Percentage positive
homosexual/bisexual males	668	4	0.6
heterosexual males	4135	32	0.8
heterosexual females	3035	10	0.3
injecting drug users	148	72	49

This study suggests that sexual intercourse can transmit HCV. However, the likelihood of infection is, the authors say, “extremely low”. As a result, they suggest targeting interventions to prevent HCV’s spread at drug users[21].

vertical transmission

Vertical HCV transmission - from mother to their babies - offers another possible route of infection. Again, however, the risk of vertical transmission seems to be relatively low. Researchers29 at the MRC Biostatistics Unit, Institute of Public Health, Cambridge, estimated the prevalence in Scotland of injection-related HCV carriers and infants infected from their mothers. Table eight summarises the findings.

Table 8: The prevalence of injection-related HCV carriers and infants infected from their mothers in Scotland

Group	central estimate	inner uncertainty
Injection-related HCV carriers	39,000	16,000-59,000
HCV infected infants	260	110-1100

The consensus statement of the European Association for the Study of the Liver (EASL) cites it as less than 6%, with a greater risk of transmission seen in women with high levels of viraemia or HIV co-infection[2]. The authors also stated that HCV transmission was unaffected by both mode of delivery, whether via Caesarean section or vaginal, and whether the child was breast-fed or not[2].

One factor that does seem to make a difference, however, is whether the mother is an injecting drug user. According to a multi-centre study in Italy, of 1372 mothers positive for HCV antibody, 98 of the offspring were infected with HCV[30]. The authors suggested that those who inject drugs are subject to repeated superinfections with different variants of HCV that may increase the rate of infection of offspring[30].

healthcare workers

The risk associated with occupational exposure to HCV (ie from needle stick injuries or contaminated biological samples) is not well-established. Gerberding[31] talks about HCV infection being more common amongst healthcare workers than in the general population and highlights a reported exposure of 3 out of 110 Japanese healthcare workers to blood containing anti-HCV antibodies during needle stick injuries and viral transmission in 7 out of 68 persons parenterally exposed to blood containing HCV RNA.

In the UK, it is estimated that the risk of transmission of HCV from a patient to a health care worker following a needle stick injury is between 1 and 5 percent. However, many healthcare professionals do not seem to be fully aware of the risk. In its *Guidance for Healthcare Workers: Protection against Infection with Blood-Borne Viruses*, the DoH sets out clear guidance on reducing the risk of transmission of HCV for all health care workers.

Scoular and colleagues[32] found that 71 per cent of 108 people from clinical and allied professions completing a questionnaire in a large teaching hospital believed that they had sufficient knowledge about blood borne infections for their clinical practice. However, many gave wrong answers or admitted being uncertain about the risk of infection with HIV, HBV and HCV. For example, around 30 per cent incorrectly identified the risk of infection with HCV following needle stick injuries, while approximately 40 per cent were unsure.

Nevertheless, many healthcare workers report being exposed to potentially hazardous situations. Indeed, 34 per cent reported contacting the occupational health department for advice because they believed that they had been at risk of exposure to blood borne viruses. The risk was especially high in clinical and laboratory areas, where 46 per cent suggested that they might have been at risk. The authors comment that these figures are higher than those in previous studies, which suggests that needle stick and other injuries might be under-reported. However, 63 per cent disagreed with the General Medical Council's guidance on blood borne infections. The authors concluded new and existing staff need to be better informed about blood borne infections[32].

HCV: morbidity and mortality

Most of the morbidly and mortality associated with HCV arises after several years, even decades. However, the mean incubation period for HCV is seven weeks[3] when changes in liver enzymes (serum aminotransferase) might be apparent. After several weeks, the body raises antibodies against HCV. However, in some cases detectable levels of antibodies against HCV can take between 3 and 6 months to emerge. Moreover, immunosuppressed people, such as those with AIDS or receiving therapy to prevent rejection following an organ transplant, might not express HCV antibodies[14].

Few patients infected with HCV develop acute symptoms. For example, only around a quarter of people with acute HCV develop jaundice[33]. Any symptoms of acute HCV resolve within 2 to 12 weeks. Around a quarter of people infected with acute HCV clear the infection. However, in between 60 and 80 per cent of cases the acute infection does not resolve[13].

Over the longer term, around 1 to 3 per cent of patients with chronic HCV clear the virus each year. Some people with chronic HCV endure non-specific symptoms such as fatigue, muscle aches, anorexia and nausea. In his study on the effects of chronic HCV infection on patients' quality of life, Foster[34] found that 14 per cent of patients had significantly impaired quality of life irrespective of the severity of liver disease as measured by short form 36 (SF36) symptomatology questionnaire. Later in the diseases natural history, chronic liver disease can lead to muscle wasting, fluid retention, bruising, jaundice and itching[3].

Meanwhile, many patients with chronic HCV develop liver fibrosis. A pathological study[35] of 397 initial liver biopsies revealed several risk factors for fibrosis (see table 9), which seemed to be correlated with high alcohol use. Moreover, 1 per cent of patients with chronic HCV develop cirrhosis each year33. So after 20 years, around 20 per cent of patients have cirrhosis[4]. Moreover, between 1 and 5 per cent of patients with chronic HCV, develop hepatocellular carcinoma each year[18]. Indeed, the increasing incidence of hepatocellular carcinoma in Japan and USA seems to reflect the rise in HCV cases. This might suggest that the morbidity from HCV will rise over the next 30 years in the UK[13]. Men over 55 years of age and those who abuse alcohol are especially likely to develop hepatocellular carcinoma associated with chronic HCV[36].

Table 9: Results of multivariate analysis of factors predicting fibrosis in HCV-positive people

Positive associations	
	Age over 40
	Evidence of previous HBV infection
	Higher necroinflammatory grade
Negative associations	
	Sex
	Viral genotype
	Maximum known alcohol intake
	Estimated duration of HCV
	Mode of transmission

As a result, HCV markedly undermines patients' quality of life. For instance, in one study[37] of 353 patients with various chronic liver diseases - hepatitis B and C, cholestatic disease or hepatocellular disease - health-related quality of life in patients was lower than the general population. Indeed, the impairment in health-related quality of life was similar to that in patients suffering from chronic obstructive pulmonary disease or congestive heart failure. Health-related quality of life declined further in older people and those with more severe liver disease.

Apart from undermining quality of life, HCV is associated with an increased risk of mortality. For example, the Trent HCV Study Group[35] examined outcomes in 1128 HCV-positive people managed and followed according to a common protocol. Mortality among the HCV-positive people was higher than expected given the age and sex distribution: 66 (5.9 per cent of cohort) died during follow up. In 31 cases, mortality arose from liver disease. In other words, 2.7 per cent of this cohort died from liver disease and this cause accounted for 47 per cent of total deaths in this group.

However, studies such as this, although informative, illustrate a fundamental problem with most of the information about morbidity and mortality associated with HCV: the data tends to be gathered retrospectively from patients with established liver disease. As a result, the data tends to be skewed towards those patients with severe disease.

The HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) Trial, which began in 2000, aims to determine whether pegylated interferon alfa 2a will decrease HCV disease progress among non-responders to a second course of anti-HCV therapy over 3½ years. The trial was set up by the National Institute for Diabetes and Digestive Kidney Diseases (NIDDK) at the National Institute of Health (NIH) and recruited from ten centres in the US. Results are expected in 2004.

However, prospective studies of, for example, people exposed to contaminated immunoglobulin may not be appropriate for extrapolation to the wider population and might underestimate HCV's impact. As a result, the rate of development of chronic liver disease and hepatocellular carcinoma is poorly characterised[38].

Against this background, a recent study[38] overcomes some of these limitations and characterises HCV's clinical course in the 10 years following infection. The study enrolled 924 people infected with HCV from a blood transfusion as well as 475 controls. The latter received a transfusion, but did not contract HCV. This study found that:

- All-cause mortality did not differ significantly different between patients and controls (Cox's hazards ratio 1.41).
- Patients were more likely to die from causes related to liver disease than controls (Cox's hazards ratio 12.84).
- Patients were more likely to die directly from liver disease than controls (Cox's hazards ratio 5.78). However, this difference did not reach statistical significance. Moreover, 40 per cent of patients who died directly from liver disease consumed excessive amounts of alcohol.
- Liver function was abnormal in 37.2 per cent of patients. Moreover, 13.9 per cent suffered physical signs or symptoms of liver disease. Several factors emerged as being associated with an increased risk of developing liver disease (see table 10).
- Ninety-one per cent of patients who underwent liver biopsy showed abnormal histology. Ten per cent showed cirrhosis.

Factor	Odds ratio
HCV RNA positive	6.44
Infection age > 40 years	1.80
Years since transfusion	1.096 per year
Women (severe disease only)	0.38

The authors concluded that HCV did not markedly influence all-cause mortality during the ten years following infection. People infected with HCV were more likely to die from liver disease, especially combined with excessive alcohol consumption. However, this difference did not reach statistical significance. Nevertheless, the authors comment that as the survival curves groups were diverging by the end of follow up, the difference in mortality between people with chronic HCV and controls may increase in the future[37]. Further follow up of this important group of patients should help better define the long-term prognosis for people with chronic HCV.

treatment recommendations

The increasing recognition that HCV represents an important cause of morbidity and mortality, combined with the growing and persuasive body of evidence that treatment is clinically efficacious and cost-effective lead to Health Technology Assessment organisations advocating combination therapy. For instance, NICE advocates treating three groups of patients with combination therapy:

- All interferon-naive and relapsed patients for six months.
- Patients with genotype 1 for an additional six months if viral load is below the level of detection after the first six months.
- Patients - such as those with haemophilia - in whom liver biopsy carries a “substantially increased risk” of adverse outcomes. These patients should be treated on clinical grounds without histology.

The former Scottish Health Purchasing Information Centre[39] (SHPIC), now replaced by the Health Technology Assessment Board, reached similar conclusions recommending that “combination therapy should replace treatment with interferon alone in chronic hepatitis C”. In particular, they recommend:

- Interferon-naive patients with at least three factors predicting a good response should receive combination therapy for six months.
- Interferon-naive patients with two or fewer factors predicting a good response should receive combination therapy for up to 12 months.
- People who relapsed following interferon alone should receive combination therapy for six months.

In April 2002, the Scottish Medicines Consortium (SMC) completed its assessment of pegylated therapy and recommended pegylated interferon alpha 2-b as an appropriate treatment for the management of hepatitis C patients[40].

NICE suggests clinicians need to assume that patients receiving combination therapy are unlikely to experience drug interactions, not be re-infected and will comply with treatment. However, the guidance notes that *former* injecting drug users, including those on oral maintenance therapy, should not be excluded. On the other hand, heavy drinkers are not generally suitable for treatment. However, these rules also seem to suggest that current addicts should not be treated.

Clearly, this guidance excludes a large proportion of the patient group that could potentially benefit from interferon. However, there is evidence that changes to service structure can allow injecting drug users to be successfully treated with HCV medication. For example, experience in other countries suggests that using alternative strategies to rigid hospital appointments - such as outreach clinics - can improve attendance and adherence to HCV medication among injecting drug users. Indeed, Backmund and colleagues[41] concluded that injecting drug users can be treated successfully with combination treatment, provided that they are supervised closely by specialists in hepatology and addiction. He hypothesised that injecting drug users with chronic HCV infection could be treated successfully without insisting on a prior drug free period of 6 to 12 months. Thirty six per cent had a sustained virological response with patients with genotype 2 or 3 having the highest percentage of sustained response. Although 80 per cent of patients had a relapse, many patients had a sustained response, even when continuing to inject illegal drugs.

the economic burden of hepatitis C

Engaging and treating high-risk groups, such as injecting drug users, is essential to ensure that the NHS is not overwhelmed by the late consequences of HCV infection. Indeed, HCV already imposes a heavy resource burden on the NHS, as table 11 shows. Several points are worth highlighting:

- Chronic HCV accounts for more than twice the case load of acute infection. However, the numbers of bed days are similar reflecting longer admissions for acute symptoms.
- Chronic HCV is the main driver of the burden of chronic viral hepatitis. HCV accounts for 81.6 per cent of the chronic viral hepatitis cases and 70 per cent of bed days.
- Most cases of chronic and acute HCV occur in men and most patients are in the prime of life.
- Most people wait around a month for an elective admission for chronic HCV. However, relatively few patients present as emergencies.
- The liver cancer statistics cover all causes. However, 1-5 per cent of people with chronic HCV progress to cancer, equivalent to between 23 and 117 cases of cancer. We can assume that between 0.4 and 2.2 per cent of the cancer cases arise from HCV.

Table 11: the NHS Hospital Episode Statistics for 2000/2001 for HCV and related diagnoses

Statistic	Acute HCV	Chronic HCV	ChronicViral hepatitis	Cancer of liver and bile ducts
Finished episodes	986	2340	2868	5186
Proportion of episodes admitted (%)	89	95	95	79
Proportion Male (%)	65	66	67	61
Proportion Emergency admissions (%)	21	9	10	40
Proportion elective admission from waiting list (%)	59	53	53	32
Mean waiting time (days)	44	60	58	13
Median waiting time (days)	26	39	37	7
Mean length of stay (days)	6.3	3.3	3.7	11.7
Median length of stay (days)	2	1	1	7
Mean age (years)	42	44	44	59
Proportion aged 15-59 years (per cent)	89	86	85	28
Proportion aged 75+ years (per cent)	2	1	1	26
Proportion day case (per cent)	40	51	49	19
Bed days	3181	3445	4913	37,466

Despite these startling statistics and NICE guidance[10] on appropriate treatment access to treatment for many of those patients who would benefit is denied[42] as, not surprisingly, the costs of paying for the resources needed to treat HCV are considerable. For example, according to the Hospital Episode statistics, the NHS performed 466 liver transplants in 2000/2001. HCV accounts for 30 per cent of liver transplants[2]. So around 140 of liver transplants arose from HCV. The British Liver Trust estimates that, excluding the cost of follow up and immunosuppressants, liver transplants for cirrhosis and cancer in people with chronic HCV cost more than £22 million between 1996 and 2000. Moreover, the NHS managed 3796 cases of liver cirrhosis and fibrosis during 2000/2001. If the proportion of people who develop end stage cirrhosis is the same earlier in the disease, 1518 arose from HCV.

HCV also appears to increase general healthcare costs. Steinke and colleagues[6] found that people with HCV were more likely than the general population to be hospitalised. People with HCV also tended to need longer in-patient stays, but showed higher mortality than the general population over six years. As a result, liver disease increased both the costs per admission and per patients.

Steinke[6] has looked at the economic burden of viral hepatitis in an observational population based study in Tayside, Scotland. He looked at the results of hospital admissions and cost analysis for each viral hepatitis group and their comparators. The median cost of HCV was £1626 more per admission £1671 per patient than the comparator group (see table 12).

Table 12: Hospitalisation admission analysis of hepatitis C subjects with general population controls

Hospital admission variable	HCV cases and controls	
	Cases (n)	Controls (n)
A No of patients	469	938
B No of patients admitted	371	544
C No of admissions	2224	1420
D No hospital admission reported	98	394
Average no of hospital admissions (C/A)	4.7	1.5
Readmissions to hospital per patient (C-B)/B	5.0	1.6
Discharged to		
Home	1795	1326
Died in hospital	15	8
Other (transfer to other hospital)	222	24
Length of stay (LOS)		
Average LOS per hospital stay (days)	5.46 (8.38)	4.61 (8.77)
Median (range) days 3 (1-138)2(1-132)		
E Total cost of admitted cases	£2,775,646	£1,638,175
Average cost per patient (E/A)£5918£1746		
Average cost per patient admitted (E/B)	£7482	£3011
Average cost per admission (E/C)	£1248	£1154
Media cost per patient admitted	£2931	£1305*
Median cost per patient	£1934	£263*

Wilcoxon test of significance, *p<0.05

An American study[43] offers an impression of the cost distribution in 191 patients with chronic HCV treated between 1995 and 1997. Figures from different countries and health care systems cannot be directly extrapolated to another country. Nevertheless, the study offers a broad brush stoke impression of the cost distribution that commissioners could apply to their trusts. The authors estimated that the total cost of care and resources used was approximately $7.5 million. As table 13 indicates liver transplantation accounts for a disproportionate cost. Drugs, even interferon, represent a relatively small percentage of the total cost. This suggests that keeping even a few patients out of hospital or avoiding the need for liver transplantation could offset much of the cost of interferon therapy.

Table 13: Examples of resources used by 191 people with chronic HCV

Resource	Number using resource	Cost ($)	% of total
Hospitalisation	60	3,788 893	50.5
Liver transplant	11	1,957 717	26.1
Out patient	189	1,553 469	20.7
All drugs	179	955 135	12.7
Ambulatory office	191	510 077	6.8
In patient biopsy	11	468 253	6.2
Interferon	98	372 066	5.0
Other sites	145	282 261	3.8
All laboratory tests	189	106 105	1.4
Out patient biopsy	112	66 313	0.9
Emergency	101	60 631	0.8

*** Some patients underwent more than one procedure**

Indeed, a growing body of evidence from around the world suggests that combination therapy is cost-effective. For example, a UK economic analysis[10] used three large randomised controlled trials of combination therapy (interferon alfa and ribavirin) to model 1000 patients who were followed over 30 years. Results of these trials indicated that larger sustained response rates are achieved with combination therapy than monotherapy, but at what cost?

Shepherd's analysis assumed that four weeks treatment with interferon alfa 3 mU three times a week and ribavirin costs £194 and £543 respectively. Thus, six months of combination therapy costs £4422, excluding monitoring costs. Based on this, the authors estimated that the additional discounted cost per quality-adjusted life-year (QALY) gained from six months combination therapy in an interferon alfa-naive patient is £7578 when compared to no active treatment. For a relapsed patient, the estimated additional discounted cost per quality-adjusted life-year (QALY) gained from six months combination therapy is £3503 when compared with interferon alfa alone.

These figures are within those considered by NICE to be cost effective. However, cost effectiveness depends on the likelihood of a sustained response. A sensitivity analysis looking at the presence of 'favourable response factors' in HCV patients, demonstrated that it was cost effective to treat all patients with combination therapy as first line treatment irrespective of how many of these factors were present. The authors concluded that it was not cost effective to continue treating beyond six months those patient with no favourable response factors, as only 8 per cent responded after six month's therapy and the cost per QALY of an additional treatment 6 months' would be around £300 000. Similarly, the former Scottish Health Purchasing Information Centre[39], estimated that the marginal cost per life year saved was between £3000 and £10 000. This, the SHPIC noted, "is within the range of other accepted NHS activities".

Nevertheless, such studies have a relatively narrow focus on healthcare costs alone. Indeed, the Royal College of Physicians (RCP) guidelines comment that future economic studies should include the indirect costs to patients; resources used in primary care and community services as well as improved outcomes, such as quality of life. Such an analysis would, presumably, further underscore the cost benefit of using combination treatment in patients with chronic HCV.

NICE estimate that implementing the guidance will cost £18 million for the first three years - to deal with the backlog of untreated cases - and then £5 million annually. However, this assumes a static rate of consultation. As the number of cases rises, this is likely to underestimate the ongoing financial burden.
On the other hand, the uncertainties surrounding HCV's epidemiology and natural history makes estimating the infections future public health impact difficult[13]. Nevertheless, US projections[43] suggest that by 2008 the number of patients:

- Requiring liver transplants will increase by 528 per cent.
- With decompensated liver disease will increase by 279 per cent.
- With hepatocellular carcinoma will increase by 68 per cent.
- Suffering from cirrhosis will increase by 61 per cent.

Assuming the same applies to the UK and based on the 2000/2001 Hospital Episode Statistics, the number of liver transplants could increase from 466 to around 2460, assuming sufficient organs and the number of liver cirrhosis and fibrosis cases will increase from 3796 to around 62223. It is difficult to extrapolate the costs accurately but some idea of the financial implications can be gained from looking at liver transplants alone. Using the figure quoted in the CMO's report[1] of £50 000 per liver transplant, we can estimate that the spend on liver transplants to be £123 million in 2008. Therefore, it has never been more important to optimise HCV services to as a matter of urgency in order to manage the increased costs.

elements of an ideal service

Recent health reforms have tried to move away from competition and more towards partnerships where health professionals and managers develop networks. The concept of these `managed clinical networks' where multidisciplinary groups agree policies and pathways for the delivery of care, lends itself well to the management of HCV infection. Networking could be one of the options for addressing the issues of specialist commissioning over larger geographical areas, complex service problems across boundaries and medical advances and new information technology impacting on clinical practice and communications.

The uncertainty surrounding HCV management suggests that treatment should be reserved for specialist centres using agreed protocols[39]. Liver transplantation is nationally commissioned and funded through the National Specialist Commissioning Advisory Group[45]. However, commissioning bodies can help ensure that local services meet certain minimum standards, perhaps by agreeing contacted standard, local protocols and pre-referral checklists.

The National Specialised Services Definitions Set (NSSDS) working party suggested HCV should be managed in specialist centres able to diagnose and treat the infection as well as offering structured follow up. It recommended that the service should include[45]:

- Hepatologists, or in some centres, infectious disease specialists.
- Specialist hepatitis nurses / nurse consultants.
- Dedicated liver histopathology services.
- Appropriate virology.

Moreover, injecting drug users may need management in collaboration with the drug addiction centre. The service should also:

- Select patients for treatment based on established guidelines. This includes evaluating the nature of the virus and the severity of the liver disease, based on histology. Liver biopsy can take place in the referring unit or specialist centre depending on expertise. However, management decisions should be taken by specialists.
- Treat patients who meet the established criteria with antiviral drugs. Patients should be monitored during treatment for response and side effects.
- Collect data on patients with viral hepatitis in the area, monitor outcomes in treated and untreated patients as well as screen to detect liver cancer early.
- Take part in clinical trials of new antiviral drugs.

In particular, given the cost of therapy the NSSDS working party suggests that liver units should employ a case identification and audit system, similar to that used in renal services. Their current databases of specialist liver work and pathology could be standardised and linked to the public health system. As HCV eradication is rare, a number of other outcome measures (see box) could be used[46] to monitor outcome (see table 14).

Table 14: Outcome measures in hepatitis C viral infection

Biochemical	Alanine aminotransferase Fibrosis markers
Virological	Viral load * Quantity **
Histological	Activity Fibrosis
Symptoms	Fatigue Quality of life
Morbidity	Haemorrhage Hepatic insufficiency Cancer
Other	Mortality Transplantation

*** Using Polymerase chain reaction for HCV RNA**
**** Using branched DNA signal amplification pathway or Polymerase**

Moreover, the liver centre and local public health officials need to collect information to predict future caseload. Table 15 summarises some data sources that should help public health officials project the cases load arising from the severe sequelae of HCV, particularly among injecting drug users[7]. The authors recommended a common HCV diagnosis report form to improve the collection of this key information. In particular, they highlight:

- The importance of collecting the year in which the patient started to inject.
- The need for updated surveys of uptake of HCV tests in current and former injecting drug users. Alternatively, developing a master index of, and collecting risk factor information about, all people undergoing HCV tests.
- Injector surveys should ask about typical frequency of sharing of needles and injecting paraphernalia over four weeks this year, last year and during the first year that they injected drugs of abuse.
- A store of historical samples from injecting drug users allowing retrospective, anonymous testing for HCV antibodies.
- Uptake and outcome in carriers treated with combination therapy for HCV.

Table 15: Data sources allowing projection of cases load arising from HCV's severe sequelae in injecting drug users.

Aspect	Data source
Diagnosis	Register of confirmed HCV infections Surveys of uptake of HCV tests by injecting drug users and others Documentation of pregnancy and outcome by injecting drug users and others
Prevelance and incidence	Anonymous testing for HCV antibodies in blood or saliva in subgroups, such as blood donors, pregnant women, healthcare workers, etc Historical data on HCV prevalence among injecting drug users HCV incidence among injecting drug users Uptake of harm reduction measures by injecting drug users
Monitoring, investigating and treating late saquelae	Linkage surveillance on, for example, death, hospitalisation rates and cancer in HCV positive people Surveys of HCV status (in patients undergoing liver biopsy as well as those with cirrhosis or liver cancer) Surveys of liver-biopsy rate in injecting drug users and others Uptake and outcome of interferon plus ribavirin Cohort studies of HCV progression Sample surveys of genotype in HCV positive injecting drug users Acute hepatitis B infections and vaccine uptake among injecting drug users Liver transplantation in HCV-infected patients HCV status and risk factors in deaths from cirrhosis or liver cancer
Quantifying the epidemic in injecting drug users	Number of injecting drug users HIV progression in injecting drug users Overdose and other mortality in injecting drug users Expert opinion on historical incidence in injecting drug users as well as age-distribution at initiation and duration of injecting drug use Age-distribution currently and at initiation to check model Historical incidence in injecting drug users inferred from blood donors Mortality of former injectors Ratios of surviving ever-injectors to injectors in the last 5 years, last year and currently to check model

Need to raise awareness

Finally, there remains a need to raise awareness about HCV in the medical profession as well as among the public. Indeed, as mentioned above, healthcare professionals often do not accurately appreciate their risk of contracting HCV in the course of their work. Moreover, many do not fully appreciate the burden of illness that HCV imposes on the NHS.

For example, most GPs do not fully appreciate the impact of HCV on the NHS. This might compromise primary care-led commissioning of services for chronic liver disease. Infections are the fifth commonest reason for primary care consultation. Against this background, the PHLS asked 371 Primary Care Group Chairs, GPs in research networks, University GP collaborators and some research nurses to rate 30 syndromes, disease and organisms in terms of five criteria:

- Burden of illness in the respondent's practice.
- NHS opportunity to affect burden of illness.
- Need for better diagnostic test (s).
- Need for more evidence to base treatment.
- Need for improved treatment guidelines.

Upper respiratory tract infections emerged as the most important disease both in terms of the burden imposed on the respondent's practice and NHS opportunity to affect burden of illness. Respondents ranked chronic fatigue and ME as number one on all of the remaining three tests. Although the list from which respondents chose included viral hepatitis, this was not ranked in the top 20 illnesses for any criteria. Indeed, viral hepatitis ranked 27th and 24th respectively in terms of the burden imposed on the respondent's practice and NHS opportunity to affect burden of illness.

By way of comparison, the PHLS biennial Overview of Communicable Diseases ranked viral hepatitis 24 and 16 respectively[47]. However, the British Liver Trust believes that these relatively low rankings do not reflect the importance of HCV either now or in the future.

For example, considering that HIV and AIDS, CJD, chronic fatigue and TB all made the top 20 ranked diseases in at least one criteria, the GPs' ranking might reflect, in the less common diseases, medical and lay media attention rather than a true reflection of the burden of illness. Clearly, there remains a need to inform GPs so that they fully appreciate the importance of HCV when considering local health needs. Steps towards this have been taken by the Department of Health with resource packs for healthcare professionals available on its website. There is a briefing on HCV, a fact sheet for use with patients and a Q&A covering symptoms, transmission, diagnosis and treatment. A series of regional seminars have also been organised to support dissemination of this information. The British Liver Trust hopes that this and other approaches will raise awareness of this devastating and increasingly common disease.

recommendations

The British Liver Trust is committed to raising awareness of HCV infection and to improving the management for HCV-infected people. There are a number of steps that need to be taken now in order to minimise the huge personal and public impact of this devastating disease.
We need to ensure that:

- there is a UK wide strategy on prevention, care and treatment against the hepatitis C epidemic. It is a priority that the current epidemic in injecting drug users is controlled and the future epidemic is prevented via the most appropriate measures in all settings.

- there are appropriate facilities for the diagnosis of hepatitis C infection and adequate referral systems in place to achieve successful ongoing management for those newly diagnosed.

- epidemiological studies of the incidence and prevalence of hepatitis C in the UK are initiated and developed, with the development of sentinel centres to monitor this epidemic and other liver diseases.

- the needs of people living with hepatitis C are investigated fully and that services for both social and healthcare are available to meet those needs. We need to facilitate equitable access to these services, ensuring that we treat patients and their disease and not social status. Representation will need to occur to maintain these services.

- guidance from NICE is implemented within the new NHS structure and that funding for both infrastructure and drug therapy is made available via managed clinical networks. It is important for hepatology, gastroenterology and infectious disease services to work together to promote continuity and consistency.

- an appraisal of pegylated interferons in combination with ribavirin is initiated and implemented to ensure that the UK is in step with a new international standard of care now.

- we create greater awareness of hepatitis C and its impact on public health across the whole population but, most importantly, those groups particularly at risk from infection.

We eagerly await the forthcoming hepatitis C strategy document for England from the Department of Health and we hope that it encompasses all our recommendations and more.
It is important that we all work together to create an accessible and comprehensive system for the diagnosis and management of hepatitis C infection and that we do it now.

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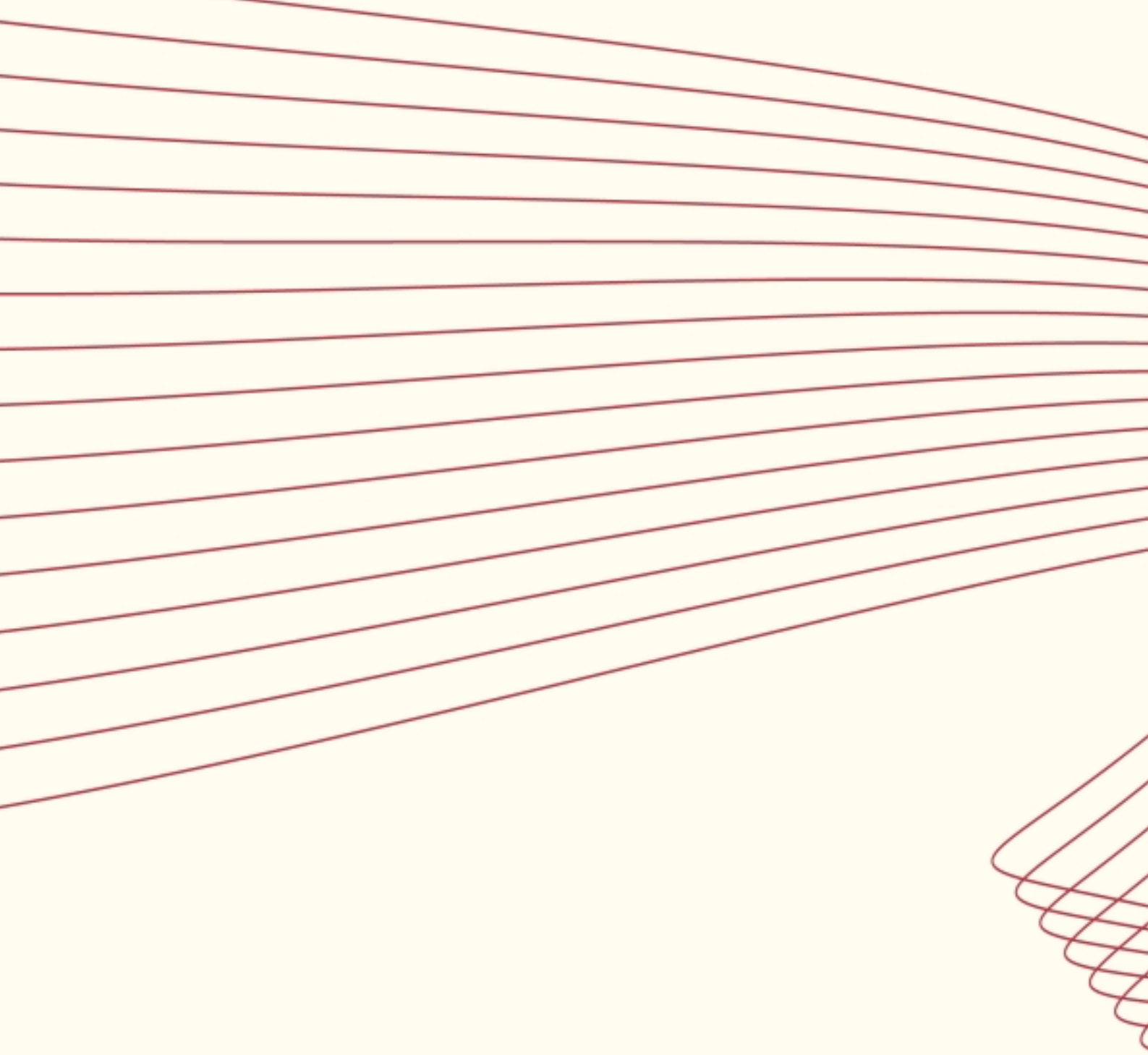

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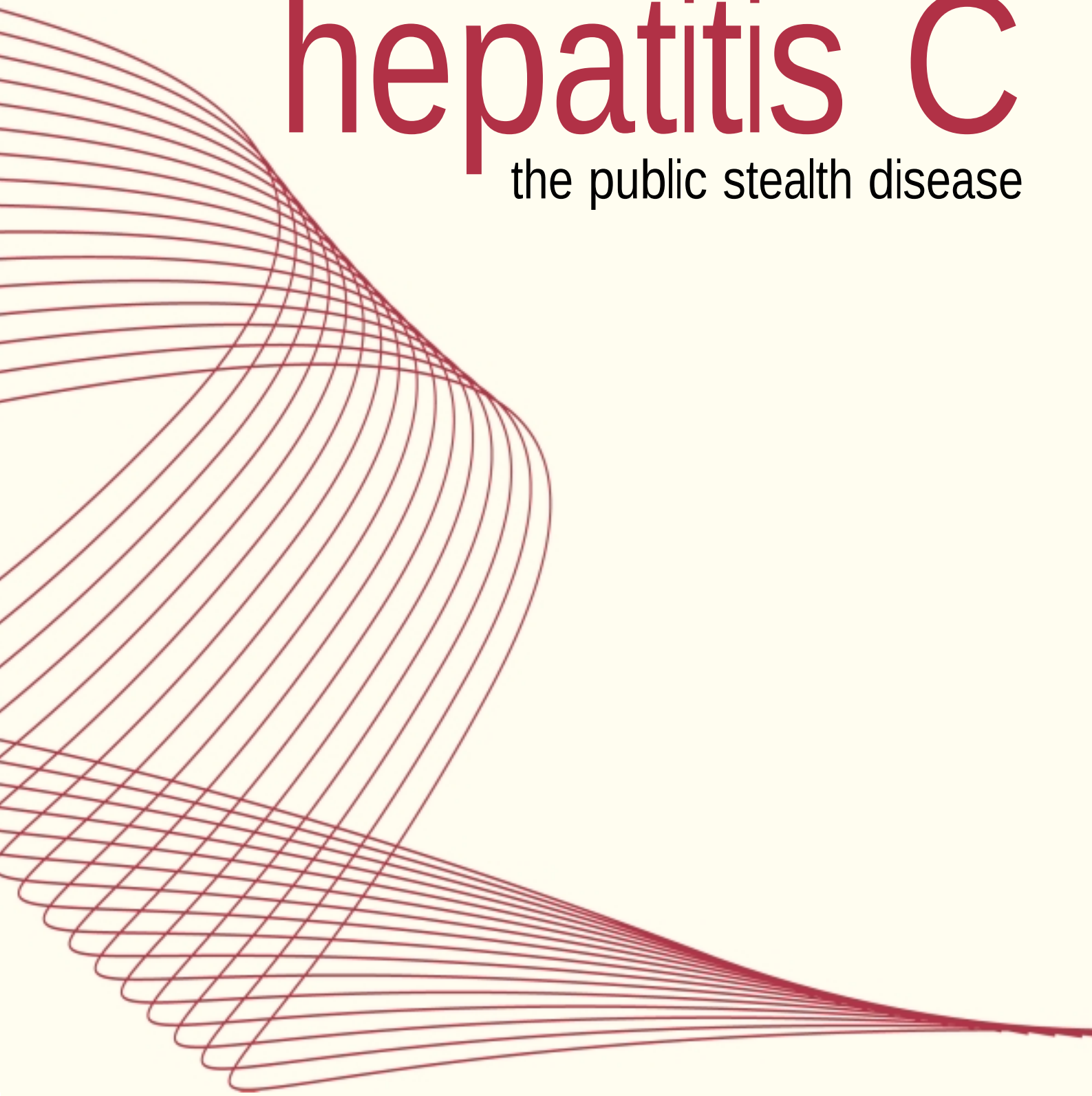

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