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1. Introduction

2. HBV: The basics

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Chronic hepatitis B - unseen and ignored

Chronic hepatitis B is not seen as a public health priority. In spite of the substantial clinical and economic burden, chronic hepatitis B currently lurks in the shadows, missing out on the publicity, awareness and financial support given to other diseases.

About the hepatitis B virus

Hepatitis B is a potentially fatal liver disease caused by the hepatitis B virus (HBV). HBV infection can cause both acute and chronic disease. Acute hepatitis B is liver inflammation lasting one to six months that infrequently leads to liver failure (“fulminant hepatitis”). Chronic hepatitis B comprises a lifelong infection characterised by liver inflammation and damage that can lead to morbidity and in some cases mortality from cirrhosis and liver cancer.

How the virus is transmitted

HBV can be transmitted in a variety of ways and is thought to be 100 times more infectious than HIV. Worldwide, the most common route of infection is vertical transmission from mother to infant at birth, although in the UK this is prevented through vaccination of babies born to infected mothers. The virus is found in the blood and other bodily fluids, and can therefore be transmitted through injecting drug use with shared syringes and needles, as well as other injecting equipment, unprotected sexual intercourse, accidental needlestick injuries in healthcare workers and transfusion of infected blood products or transplantation of infected organs in countries where there is inadequate or no donor screening. Body piercing and tattooing may also pose a risk from poorly or unsterilised equipment.

The burden of infection

Worldwide, 350 million people are chronically infected with HBV and one third of the world’s population have been exposed at some point in their lives. Each year, hepatitis B kills between 500,000 and one million people. Internationally, hepatitis B is second only to tobacco as a human carcinogen, causing 50% of all liver cancers.

Although the UK has a much lower prevalence than many other countries, the Department of Health estimates that around 180,000 people in the UK are currently suffering from chronic hepatitis B. In addition, there are at least 1,300 cases of symptomatic acute hepatitis B each year and 7,700 new cases of chronic hepatitis B. Of these new chronic cases, around 300 people were infected within this country, while the remainder, some 96%, have entered this country, generally from areas of high prevalence where HBV is frequently transmitted from mother to child. Many people with asymptomatic infections are also infectious, and quite often remain undiagnosed until they present with overt disease.

The cost of chronic hepatitis B

There are no robust estimates of how much treatment of chronic hepatitis B costs the NHS. Calculations based on an ongoing Scottish audit of patients with hepatitis B and a German costing study suggest
that treatment of chronic hepatitis B could cost the NHS between £26 million and £375 million. The lower estimate is based on an estimate of diagnosed patients, and includes hospital costs only, while the upper estimate is based on all patients being diagnosed and treated, which is currently not the case.

**Preventing hepatitis B with vaccination**

The vast majority of new infections could be prevented through vaccination. Worldwide over 150 countries have implemented universal vaccination of newborns and/or adolescents. At present in the UK, vaccination is offered selectively to healthcare workers, babies born to infected mothers and selected high-risk groups, such as men who have sex with men, sex workers and injecting drug users. However, even within these groups coverage is poor, demonstrating the need for a reappraisal of vaccination policy.

**Availability of tolerable and effective treatments**

Acute, symptomatic hepatitis B is usually self-limiting and requires only convalescence care. However, there are now a number of tolerable and effective treatments for chronic hepatitis B for many, but not all patients, such as Interferon-alpha, Lamivudine (Zeffix) and Adefovir dipivoxil (Hepsera). These treatments stop the virus from replicating thereby making the person less infectious, preventing liver damage and disease progression and enabling the patient’s immune system to fight the virus effectively. However not all patients respond, and in the case of Lamivudine, viral resistance is an increasing problem. In addition, many new treatments are under development. Despite this only a minority of patients are currently receiving treatment, an estimated 1,500 per annum.

**A call to action: UK-wide strategy required**

The Foundation for Liver Research calls for a UK-wide strategy for the prevention, diagnosis and treatment of chronic hepatitis B. Each region should introduce and follow local protocols and treatment algorithms/procedures for the screening, diagnosis, referral, management and follow-up of patients with chronic hepatitis B. They should also commission appropriate facilities to implement and evaluate these protocols via managed clinical networks.

There is also a need for further research to obtain accurate assessments of the incidence, prevalence and economic burden of chronic hepatitis B in the UK. The Foundation also calls for policymakers, purchasers, service providers and physicians to investigate the needs of people living with chronic hepatitis B and ensure that health and social care services meet those needs. Access to these services must be equitable: at present there are large geographical disparities in care and many of those suffering from chronic hepatitis B are within the poorest sections of our community.

Hepatologists, gastroenterologists and infectious disease specialists must work together in partnership with general practitioners to ensure efficient and effective management of chronic hepatitis B. The Foundation for Liver Research believes that there is a need for more training of primary care staff to increase awareness of the disease and current treatment options. The Government, the media, charities and healthcare workers need to increase awareness of chronic hepatitis B across the whole population to ensure that this disease moves out of the shadows.
1. Introduction

Hepatitis B virus (HBV) causes severe liver damage and can frequently cause death from liver failure or cancer. Yet chronic hepatitis B lurks in the shadows failing to attract either the research funds or the attention from purchasers, service providers and the media that it deserves. For example, HBV is one hundred times more infectious than HIV in blood or body fluids, and is thought to be able to survive in dried blood for in excess of a week [Lin, 2004]. Worldwide, 350 million people are chronically infected with HBV (Lavanchy, 2004) and its complications kill between 500,000 and one million people each year (de Franchis et al, 2003; Lin and Kirchner, 2004): between 600 and 1,200-fold more than have died from SARS (World Health Organisation, 2003).

In the UK, chronic hepatitis B remains a cause of considerable suffering as well as imposing a heavy burden on the NHS. The Department of Health estimates that 0.3% of the UK population is chronically infected with hepatitis B, equivalent to some 180,000 people (Department of Health, 2002a). In contrast, only between 1,300 and 16,000 people are thought to harbour the human form of BSE (Hilton et al, 2004). There are around 1,300 new cases of acute hepatitis B reported in the UK each year - roughly three a day. We estimate in this report that acute and chronic hepatitis B could cost the NHS between £26 million and £375 million.

In some people, acute HBV infection causes unpleasant, distressing symptoms. However, most patients with chronic hepatitis B do not realise that they have been infected until years later when they develop cirrhosis, end stage liver disease or liver cancer. For instance, patients with chronic hepatitis B (CHB) are some hundred times more likely to develop hepatocellular carcinoma than those who are not infected (Ganem and Prince, 2004). HBV also causes cirrhosis. Across all causes (which include alcohol and hepatitis C), cirrhosis kills more men than Alzheimer's disease and more women than cervical cancer in the UK (Vass, 2001). In the meantime, people with asymptomatic CHB can spread the virus through sexual contact, vertical transmission from mother to baby or exposure to blood (e.g. through injecting drug use or occupational needle stick injuries).

Transmission of this infection could be prevented through vaccination - especially if combined with screening and public health campaigns to alter risk behaviour. A growing number of treatments can control the disease and prevent potentially fatal complications. However, current NHS commissioning arrangements mean that services to prevent and treat liver diseases - including CHB - are often inadequate. As a result, there is a risk that many patients will not benefit from these advances.
Against this background, the Foundation for Liver Research aims to raise awareness of this potentially devastating disease and subsequently reduce the level of deaths and disability associated with chronic hepatitis B. The growing number of effective treatments currently on the market (or in development) and a forthcoming technology appraisal by the National Institute for Clinical Excellence give this report extra urgency.

The purpose of this report is twofold. To influence policy makers and their advisors to push chronic hepatitis B up the agenda and to inform commissioners, purchasers, providers and the public about this condition and its management.

The Foundation hopes that the report might help hepatologists, gastroenterologists and infectious disease specialists develop a business case with their local NHS Trusts and Primary Care Trusts to fund improved service provision. It is time chronic hepatitis B moved out of the shadows.
HEPATITIS B: Out of the shadows

2. HBV: The basics

Summary: This chapter introduces HBV, its characteristics, biology and life cycle as well as the acute and chronic manifestations of the infection. Recent years have shown marked progress in many of these areas. Researchers’ increasing understanding of HBV has yielded a growing number of targets for innovative treatments as well as a better understanding of the disease.

2.1 The hepatitis viruses

Clinical and epidemiological studies conducted in the 1940s, 1950s and 1960s gave the first hints that acute hepatitis could arise from several causes (Ganem and Prince, 2004). Nevertheless, it was 1965 before Krugman and colleagues established beyond reasonable doubt that there were at least two types of hepatitis – one of which (originally termed "serum hepatitis") came to be known as hepatitis B (Ganem and Prince, 2004).

Further work revealed the “antigen” (a protein capable of triggering an immune response) in the blood of patients suffering from leukaemia, leprosy and hepatitis (Ganem and Prince, 2004). Another group of researchers independently discovered an antigen in the blood of patients who developed hepatitis following blood transfusions. The two antigens were later found to be identical and this protein is now known as the hepatitis B surface antigen (HBsAg). The discovery led to a blood test for HBV, which is considered later.

HBV is one of six viruses currently recognised as causing acute hepatitis in humans – as shown in table 1. Some other viruses – such as Epstein Barr and Cytomegalovirus (CMV) can cause acute hepatitis, although such cases are rare. Moreover, doctors cannot identify the virus responsible in around 7% of acute hepatitis cases that are likely to be of viral cause. Therefore, it seems possible that the list of viruses capable of causing acute hepatitis will increase still further (Ryder and Beckingham, 2001a).

<table>
<thead>
<tr>
<th>Subtype</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course</td>
<td>Acute</td>
<td>Chronic</td>
<td>Chronic</td>
<td>Chronic</td>
<td>Acute</td>
<td>Not clear</td>
</tr>
<tr>
<td>Infection route</td>
<td>Orofaecal, sexual</td>
<td>Sexual, contact with blood/body fluids</td>
<td>Contact with blood, rarely sexual</td>
<td>Contact with blood, sexual</td>
<td>Orofaecal</td>
<td>Contact with blood, possibly sexual</td>
</tr>
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</table>

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<tr>
<th>Vaccine</th>
<th>Yes</th>
<th>Yes</th>
<th>No</th>
<th>Indirect from Hep B vaccine</th>
<th>No</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>Long term prognosis</td>
<td>Lasts up to six months</td>
<td>Carrier; cirrhosis; liver cancer; extrahepatic symptoms</td>
<td>Carrier; cirrhosis; liver cancer; extrahepatic symptoms</td>
<td>May exacerbate hepatitis B</td>
<td>Unknown; Up to 20% mortality in pregnant women</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 1: The types and infection routes for human hepatitis viruses.
2.2 The virology of HBV

The hepatitis viruses belong to distinct families, although they can all cause the symptoms of hepatitis. HBV belongs to a family of viruses called hepadnaviridae and stores its genetic code as a partially double-stranded circular DNA molecule. The genome and other viral proteins are enclosed within a capsule (the nucleocapsid), which is made up of the hepatitis B core antigen (HBCAg). The viral core (the nucleocapsid and its contents) is itself surrounded by an envelope containing HBsAg. The enveloped HBV particle is known as the Dane particle (Dane et al, 1970; Lin and Kirchner, 2004).

Once within the blood stream, HBV infects liver cells (hepatocytes) in preference to other types of cells within the body. After entering the cell, the core particle migrates into the cell nucleus, where the incomplete strand of the viral genome is completed to produce "covalently closed circular DNA" (cccDNA) (Ganem and Prince, 2004; Naoumov, 2003). This acts as a template for the production of "messenger RNA". Messenger RNA molecules move into the cytoplasm of the host cell and serve two purposes. Some molecules are translated into proteins needed by the virus, such as HBCAg, HBsAg, the hepatitis B "e" antigen (HBeAg) and the DNA polymerase enzyme. Another messenger RNA molecules, termed pre-genomic RNA, is packaged into the nucleocapsides and serves as a template for reverse transcription into new HBV DNA molecules.

Figure 3: The HBV virus

Adapted from Kann M and Gerlich WH. In: The Molecular Medicine of Hepatitis. 1997: 63-77
2. HBV: The basics

Most new core particles are coated with an HBsAg-containing envelope and exported out of the cell, ready to infect other hepatocytes. Other core particles are recycled back into the nucleus to produce more covalently closed circular DNA. The resulting reservoir of covalently closed circular DNA means that the viral infection tends to persist – hence the chronicity of the infection (Ganem and Prince, 2004).

The symptoms and complications of HBV infection arise from liver damage. However, HBV does not itself directly damage hepatocytes, as it is not directly cytopathic. Instead, the liver damage and symptoms characteristic of HBV seem to arise from the immune system’s attempts to remove the infection. Several types of white blood cell (cytotoxic and natural killer T-cells) fight the virus by killing infected cells, but the immune system also produces chemical messengers (cytokines), such as interferons, which appear to have antiviral affects inhibiting viral replication; reducing proliferation of viruses to infect new cells; and modulating the immune response to the infection (Ganem and Prince, 2004).

The importance of the immune system in pathogenesis means that immunosuppressed people often show only mild liver damage, despite having high levels of the virus in their blood (Ganem and Prince, 2004). Similarly, patients infected early in life are generally asymptomatic and show little liver damage for several decades despite a heavy viral load, as the immune system initially tolerates the infection and therefore causes no damage. Unfortunately this can change in later life, with a
sudden activation of the disease process, in the main due to a mutation of HBV (see also Section 2.4: Chronic hepatitis B).

The increased understanding of the mechanisms by which HBV replicates and causes disease is likely to lead to more advances in treatments in the future – a necessity for the many patients who are at increasing risk of the morbidity and mortality of this condition.

### 2.3 Acute HBV infection

Acute HBV infection rarely causes symptoms. Indeed, 70% of adults and 90% of children under five years old do not develop symptoms of acute hepatitis (Lin and Kirchner, 2004). Nevertheless, these patients may still be infectious and capable of transmitting the infection.

In patients who do develop acute hepatitis, symptoms develop during a period lasting one to six months. Patients can experience a variety of symptoms including nausea, anorexia, fatigue, low-grade fever and abdominal pain (Lin and Kirchner, 2004). About 10% of people with acute hepatitis B develop a systemic disease characterised by a rash and joint pains. Some patients (around 30%) develop jaundice (Ryder and Beckingham, 2001a) - a yellowish colouration of the skin and the whites of the eyes, accompanied by dark urine and pale stools. In general, the symptoms of acute hepatitis B clear after one to three months, although some people find that the fatigue persists for longer (Lin and Kirchner, 2004).
About 1% of people with acute hepatitis B develop marked liver damage and liver failure (fulminant hepatitis), which is fatal in 75-80% of cases (Lin and Kirchner, 2004; Pereira, 1999; Sonnenberg et al, 1999). Many of these patients need a liver transplant (Lin and Kirchner, 2004) and some may also have damage to the pancreas – the gland that produces insulin and other hormones. Occasionally, acute hepatitis can cause other serious complications including heart disease, aplastic anaemia and pleural effusion (an abnormal build-up of fluid between the pleural membranes, which cover the lungs) (Ryder and Beckingham, 2001a).

2.4 Chronic hepatitis B

In more than 95% of people who develop acute icteric ("jaundice") hepatitis B, the immune response eliminates the virus within six months to the extent that HBsAg becomes undetectable. As a result, doctors define chronic hepatitis B (CHB) based on the presence of detectable HBsAg being present for greater than six months (de Franchis et al, 2003; Lin and Kirchner, 2004).

The risk that a patient will progress from acute to chronic hepatitis B depends on the strength of their immune response. Adults tend to mount stronger immune responses than newborns. As a result, more than 90% of infants infected at birth develop CHB. The proportion of infected patients who progress to CHB declines with age: between 25% and 30% of those aged under five years develop CHB, compared with only 3% to 5% of older children and adults (Lin and Kirchner, 2004). Men seem to be more prone to developing CHB than women, although the reasons for this gender difference are unclear (Ryder and Beckingham, 2001b).

We currently recognise two types of CHB – HBeAg positive and HBeAg negative. Many people with CHB do not experience symptoms and are therefore generally unaware that they are infected. These are sometimes called "carriers", or "healthy carriers". Unlike some other diseases, HBV does not actually cause a "healthy carrier state" as a patient can still be developing the complications, albeit at a lesser rate than someone who is symptomatic. As a result, the term "carrier" is a misnomer (See also section 5: Diagnosis).

In patients infected early in life (at birth or before age five), the immune system initially tolerates the infection, which means that liver damage and symptoms of hepatitis do not arise despite the presence of high levels of viral DNA (de Franchis et al, 2003). However, after a number of years, or even decades, the immune system begins to fight the virus and signs of chronic hepatitis and liver damage arise. In patients infected as adults or older children, the immune response and symptoms of hepatitis develop much more quickly.

Over time the immune reaction leads to widespread inflammation ("hepatitis"), cell death (necrosis) and scarring (fibrosis) within the liver. This continual damage frequently leads to cirrhosis (the build-up of fibrous scar tissue in place of functional liver tissue) and hepatocellular carcinoma (primary liver cancer). Around 2-6% of patients with signs of CHB progress to cirrhosis each year (de Franchis et al, 2003; Fattovich et al, 1991; Ikeda et al, 1998) and around 0.5% develop HCC (Lavanchy, 2004). Patients who progress to disease whilst the virus expresses HBeAg are often classified as having "HBeAg-positive" disease.
Liver
Abnormal
Brain
damage,
strokes,
memory loss,
paranoia,
hallucinations

Spleen
Enlarged

Eyes
A yellowish tint to the
white part of the eye

Esophagus
Inflammation of the
esophagus with
bleeding

Muscles
Painful,
swollen

Pancreas
Inflammation

Legs
Swollen

Legs and arms
Numbness,
tingling

Figure 6: The effect
of liver disease

Skin
Jaundiced
or yellow

*Every person with liver disease
does not experience all these
effects. Some of these effects
occur only in persons with very
serious liver disease.

Figure 7: Chronic hepatitis B serology in an HBeAg-positive patient

- Chronic hepatitis B is recognised as
HBeAg-positive, or HBeAg-negative
with disease, the latter recently
increasing in prevalence across
the UK
- The consequences of chronic
infection are liver fibrosis, cirrhosis
and hepatocellular carcinoma in
variable proportions of cases,
induced by the immune response
to the infected liver
- Only 14-28% of patients with
decompensated cirrhosis will
survive beyond five years
- Following diagnosis of
hepatocellular carcinoma only 5-6%
of patients will survive beyond
five years
- Surgical interventions for both
cirrhosis and hepatocellular
carcinoma can be life saving, and
are improving
Between 10% and 30% of patients with CHB experience flares that resemble acute hepatitis B. Flares are characterised by a short-lived rise in levels of a liver enzyme (alanine aminotransferase), which is caused by the destruction of infected hepatocytes by the immune system. Since flares reflect an immune response to the virus, they frequently coincide with the development of antibodies against the "e" antigen (HBeAg). Between 8% and 15% of patients with chronic hepatitis develop antibodies (anti-HBe) against HBeAg and a loss of HBeAg each year (de Franchis et al, 2003). Raised alanine aminotransferase levels and treatments such as Interferon alpha, Lamivudine and Adefovir increase the likelihood of HBeAg seroconversion developing (de Franchis et al, 2003; Lai et al, 1998; Marcellin et al, 2003).

In general, once HBeAg seroconversion has developed, levels of viral DNA and other viral markers drop substantially, liver inflammation is reduced and the risk of disease progression is limited (de Franchis et al, 2003). However, in recent years a mutant strain of HBV that does not express HBeAg has been discovered (the so-called “precore mutant”), mainly in patients who have been infected since early childhood and who have been immunotolerant for most of that time. This is of some concern as HBeAg-negative disease appears to be increasingly common worldwide, though more prevalent in the Mediterranean region (Bonino and Brunetto, 2003; de Franchis et al, 2003; Hadziyannis and Vassilopoulos, 2001).

These patients have a particularly high risk of disease progression over time, and they are often classified as having “anti-HBe positive” or “HBeAg-negative” disease. The absence of HBeAg in these patients is often mistakenly associated with a favourable prognosis and reduced infectiousness (the misnomer, “healthy carrier”), which means that careful monitoring of aminotransferases and viral DNA levels is a requirement.
2.5 Cirrhosis

In many patients with CHB, the liver damage caused by infection and inflammation eventually leads to the replacement of functional liver tissue with fibrotic scar tissue. Such changes in liver composition are termed "cirrhosis", as they cause the liver to appear tawny coloured (cirrhosis is the extraction from the Greek word for “tawny”). Cirrhosis occurs more frequently among patients who are older, those who misuse alcohol and those infected with the HBeAg-negative mutant strain. High levels of viral DNA, more extensive fibrosis at diagnosis and concurrent infection with HIV, HCV or HDV also increase the risk of cirrhosis (de Franchis et al, 2003). In the early (compensated) stages of cirrhosis, the liver continues to function and many patients have no overt symptoms, although some experience fatigue, dyspepsia and upper abdominal discomfort.

However, cirrhosis frequently progresses to the extent that healthy liver tissue cannot compensate for the cirrhotic lesions. Around 6% of people with compensated cirrhosis undergo hepatic decompensation each year (Fattovich et al, 1997; Lavanchy, 2004). Decompensated cirrhosis comprises complete, irreversible liver failure and can only be cured through liver transplantation. Decompensation can manifest as ascites (an abnormal build-up of fluid in the abdomen), jaundice, high blood pressure within the portal vein, variceal bleeding or a combination of these complications (de Franchis et al, 2003; Fattovich, 2003). Patients with decompensated cirrhosis have a poor prognosis: only 14-28% of patients will survive for five years (Fattovich, 2003). Decompensated cirrhosis due to CHB is a significant reason for liver transplantation.

Figure 9: Natural history of hepatitis B infection

- Only 1% of patients spontaneously clear HBsAg per year, leading to complete resolution of infection – this will be a critical marker of response to therapy in the future

2.6 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) – primary liver cancer – is another serious complication caused by HBV. Patients with CHB are a hundred times more likely to develop hepatocellular carcinoma than people who resolve the acute infection. This cancer of the hepatocytes generally emerges 25 to 30 years after the acute infection (Lin and Kirchner, 2004). Research suggests that this cancer develops when hepatocytes damaged by the immune response re-generate, increasing the risk of mutations linked to cancer developing (Lin and Kirchner, 2004).

In North America, there are around 21 cases of hepatocellular carcinoma per million people in the population each year, of which 30-40% are caused by HBV or HCV (National Cancer Institute, 2002). Applying these figures to the UK suggests that there are over 1,200 new cases of hepatocellular cancer each year of which around 430 are caused by viral hepatitis. There is very little UK data on the true incidence of HCC.

Some patients in the early stages of hepatocellular carcinoma do not experience any symptoms. In others, the cancer causes vague discomfort in the upper abdomen. Some patients report loss of appetite and weight, nausea, weakness, lethargy, fever and jaundice. However, in the later stages of the disease, quality of life is greatly impaired (Bennett et al, 1997; Crowley et al, 2000; Wong et al, 1995) and only 5-6% of patients will still be alive five years after diagnosis (Boring et al, 1993).

There are various treatments for hepatocellular cancer, either surgical or non-surgical. Partial hepatectomy, in which up to 80% of the liver is removed offers a potential cure (Mor et al, 1998), but generally has poorer long term survival than transplantation, in the main due to reoccurrence (Ryder, 2003), with a five year survival of 10% to 30% (MacIntosh and Minuk, 1992; Nagorney et al, 1989; Starzl et al, 1980).

Transplantation is a potentially curative procedure in patients with small and defined tumours and cirrhosis, if the tumour size is less than 5cm in diameter, or there are only three tumours less than 3cm diameter each, and there is no secondary spread outside of the liver, but resection and transplantation both have a place dependent on patient selection (Ryder, 2003). Other treatments include injecting alcohol or acetic acid directly into the tumour or destroying the tumour using lasers, ultrasound, liquid nitrogen or other radiation. These newer treatments may improve outcomes in hepatocellular carcinoma, although further studies are needed to fully assess the role of such promising treatments and to establish their role in the management of the condition (Ryder, 2003).

The number of treatment options should increase further in the future, as researchers come to better understand the mechanisms that link HBV to hepatocellular carcinoma. In particular, future research is likely to determine the mutations and molecular changes that lead to the development of cancer. Such advances may lead to new treatments that enhance the prospects for people with liver cancer.
2.7 Resolution of CHB

Around 1% of infected individuals clear HBsAg spontaneously (HBsAg seroconversion) each year through an effective immune response leading to the development of antibodies (anti-HBs) against HBsAg (de Franchis et al, 2003; Lin and Kirchner, 2004). In these patients, viral load declines below the level of detection (if not already) and reactivation of infection is rare (de Franchis et al, 2003). Antibodies against HBsAg occur more commonly among patients who have already developed antibodies against HBeAg and several treatments are also thought to increase the probability of these hallmark changes (Wong et al, 1995). As the number of effective treatments for CHB increases, it is hoped that more people with CHB will be cured in the future (Ganem and Prince, 2004).
HEPATITIS B: Out of the shadows

3. Clinical and economic burden of HBV

Summary: Although HBV receives less publicity than some other infections, it nonetheless imposes a heavy clinical and economic burden. This suggests that HBV deserves to be considered as a higher priority by policy makers, purchasers, service providers and physicians.

HBV is one of the most common viral infections in humans. The figures are stark:

- Worldwide, 350 million people are chronically infected with HBV (Kane, 1995; Lavanchy, 2004)
- A third of the world’s population have been exposed in the past (Lin and Kirchner, 2004)
- HBV accounts for between 500,000 and 1 million deaths each year worldwide (de Franchis et al, 2003; Lin and Kirchner, 2004). These deaths arise from chronic hepatitis B, cirrhosis and hepatocellular cancer
- HBV is considered, after tobacco, the number two global carcinogen, causing 50% of primary liver cancer in the world, which is in turn the sixth most common cancer (de Franchis et al, 2003)

3.1 Acute hepatitis B

In the UK, acute hepatitis B is a notifiable disease, which means that it is mandatory for doctors to report any cases they see to the Health Protection Agency. However, any cases that are not seen by a doctor will not be reported. According to the notification system, there were around 1150 cases of acute hepatitis B in England and Wales in 2003 (Health Protection Agency, 2004), equating to around 1300 cases per year in the UK. This is almost twice the number of cases reported in 1993.

The number of acute hepatitis B cases acquired from abroad decreased between 1989 and 2002, probably due to the use of pre-travel vaccination and changes in reporting systems. Most patients who did acquire the disease abroad in recent years became infected in Europe, the Indian sub-continent, the Far East and Africa.

![Figure 10: Changing incidence of acute hepatitis B](Health Protection Agency, 2004)
Acute HBV infection is asymptomatic in 70% of adults and 90% of children under five years of age (de Franchis et al, 2003; Lin and Kirchner, 2004). If we assume that 30% of those infected show symptoms and that all symptomatic cases are reported, we calculate that around 4,300 people in the UK become infected with HBV each year. This is broadly in line with other estimates. Hahne and colleagues estimated that the annual incidence of acute HBV infection in England and Wales between 1995 and 2000 was around 0.0074% (Hahne et al, 2004). This equates to 4,400 new infections each year.

3.2 Chronic hepatitis B

The prevalence of CHB (the proportion of people with the disease at a particular point in time) varies greatly between countries. CHB has a prevalence of 8% or more in many African and Asian countries and in these countries most infections arise through "vertical transmission" from mother to child (de Franchis et al, 2003) – 45% of the global pandemic resides in these countries (Lavanchy, 2004). In contrast, North America, Australasia and Northern Europe (including the UK) have a low prevalence (less than 1%), with most infections arising through sexual contact and injecting drug use. Mediterranean countries, the Middle East and the Indian subcontinent have an intermediate prevalence (1-8%), with infections arising through a variety of routes. In developing countries it is estimated that 8-16 million HBV infections per year are caused by contaminated and unsafe injections (Lavanchy, 2004).

Unlike acute hepatitis B, CHB is not a notifiable disease, which makes calculation of the prevalence in the UK more difficult. Ryder and Beckingham estimate that 1 in every 550 people (0.2%) in the UK suffers from CHB (Ryder and Beckingham, 2001b). Some estimates suggest that prevalence of CHB is still higher. The Department of Health, for example, estimates that 0.3% of the UK population is chronically infected with HBV (Department of Health, 2002a). Based on this figure, 180,000 people in the UK suffer from CHB. Among certain sectors of the population, the prevalence is extremely high: among heterosexual men and women attending genitourinary medicine clinics, 2.4% of those born in the UK showed evidence of HBV infection. Among those born outside the UK, as many as 12% showed evidence of infection. The rate was especially high in heterosexuals born outside the UK attending the clinic with an acute sexually transmitted infection (18%) (Department of Health, 2001).

Hahne et al recently estimated the number of new cases of CHB within England and Wales (Hahne et al, 2004). They estimated that 269 new chronic infections would arise from the 3,780 cases of acute HBV infection occurring in England and Wales each year. In addition, there is a net migration of 90,220 people into England and Wales, of whom 6,571 will have CHB. Based on this data there are therefore a total of 6,840 new cases of CHB in England and Wales each year. If we apply the same estimate to Scotland and Northern Ireland, this suggests that there are around 7,700 new cases of CHB in the UK each year.

In the remainder of this document we will use prevalence estimates from the Department of Health, which suggests that 180,000 people in the UK suffer from CHB (Department of Health, 2002a).
3.3 Economic burden

Currently, there are no rigorous estimates of the economic burden imposed by HBV in the UK, although several groups have estimated the burden for Italy, USA, Germany and South Korea and a study of the burden of disease in Scotland is underway.

The Epidemiology of Liver Disease in Tayside (ELDIT) study is being undertaken to determine the prevalence, incidence and economic burden of liver disease in Tayside, Scotland (Steinke et al, 2002). The audit includes everyone registered with a Tayside general practice between January 1st 1991 and December 31st 1998. Within this population, 187 patients were found to have detectable HBsAg, suggesting that the prevalence of diagnosed CHB in this region was 0.0041%.

Hospital admissions among patients with detectable HBsAg were compared with age and sex-matched controls. People who tested positive for HBsAg were significantly more likely to be admitted to hospital and consumed more hospital resources when they were admitted (Table 2). Applying the difference in the average cost per patient (£584) and the prevalence of diagnosed CHB (0.078%) found in this study to the UK population suggests that there are 45,700 people with diagnosed CHB in the UK who consume hospital resources worth £26.7 million. In practice, it is likely that the total burden of hepatitis B is far higher than this figure suggests. Firstly, the prevalence of hepatitis B is probably lower in Scotland than in the rest of the UK and secondly this cost estimate excludes acute hepatitis B and any costs incurred outside the hospital, and only takes diagnosed patients into account. It does not estimate the burden from the significantly higher number of undiagnosed patients. Yet only an estimated 1,500 patients are treated for CHB per year.

<table>
<thead>
<tr>
<th></th>
<th>HBsAg carriers</th>
<th>Controls</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>187</td>
<td>374</td>
<td>-</td>
</tr>
<tr>
<td>Number admitted</td>
<td>117</td>
<td>222</td>
<td>-</td>
</tr>
<tr>
<td>Median cost per patient admitted</td>
<td>£2,810</td>
<td>£1,579</td>
<td>£1,231</td>
</tr>
<tr>
<td>Median cost per patient</td>
<td>£847</td>
<td>£263</td>
<td>£584</td>
</tr>
</tbody>
</table>

Table 2: Cost of managing patients with detectable HBsAg in Tayside

National estimates of the total cost of hepatitis B range from £40 million for Italy (de Franchis et al, 2003) through £520 million for South Korea (Yang et al, 2001) and £589 million for Germany (Harbarth et al, 2000) to £5.1 billion in the United States of America (Veenstra et al, 2003) (Table 3). However, the burden of chronic hepatitis B to any given country depends crucially on its population and the prevalence of hepatitis B.
Of the countries for which burden of disease estimates are available, the country with a prevalence and population most closely matching that of the UK is Germany. Germany is, like the UK, considered to have a low prevalence of CHB (less than 1%) and had a population of 82.3 million in the second quarter of 2001 - 40% larger than that of the UK (German Federal Statistical Office, 2004).

Harbarth et al estimated that the direct healthcare costs of managing acute hepatitis B were DM 7,702 per episode, while the direct healthcare cost of treating CHB was DM 4,247 per patient per year (Harbarth et al, 2000). The cost of treatment varied substantially with disease severity. By taking account of exchange rates and inflation, this study suggests that acute hepatitis B costs £3,781 per episode in today’s money, while CHB costs £2,085 per patient per year.* Taking into account the societal cost of work time lost in addition to the cost of medical care, acute hepatitis B cost DM 10,018 (£4,917) per episode, while CHB cost DM 4,860 (£2,386) per patient per year.

Harbarth et al estimated the total cost of hepatitis B in Germany to be DM 1,200 million (£589 million), based on there being 420,000 cases of CHB at any one time in addition to 30,000 cases of acute hepatitis B each year (Harbarth et al, 2000). Based on the 1,300 cases of symptomatic acute hepatitis B occurring in the UK each year, this condition costs the NHS £4.92 million and costs society as a whole £6.39 million. If all 180,000 people with CHB in the UK were diagnosed and treated, the total healthcare cost would be £375 million and the total societal cost would be £429 million. In practice, however, many patients with CHB are not diagnosed or treated, so the actual costs are likely to be far lower. If we assumed that only 60,000 patients with CHB required treatment/monitoring, as only a third will progress to significant or endstage liver disease, the total cost to the NHS would be £125 million, with a societal cost of £143 million.

Numerous economic evaluations have demonstrated that treating patients with chronic hepatitis reduces the costs associated with cirrhosis and hepatocellular cancer (Crowley et al, 2000; Dusheiko and Roberts, 1995; Wong et al, 1995), which means that doubling the number of patients who are diagnosed and treated is likely to increase costs by less than twofold.

---

* The burden of disease calculations by Harbarth et al were based on data collected in 1997. On 31st December 1996, one Deutschmark was worth £0.379 (http://www.xe.com/ict/table.cgi). Since this date, the UK Personal Social Services pay and prices index has increased by 29% Netten, A. and Curtis, L. (2003) Unit Costs of Health and Social Care 2003. PSSRU Personal Social Services Research Unit, Canterbury, UK. This means that each 1997 Deutschmark is now worth £0.49 (£0.379 multiplied by 129%).
3. Clinical and economic burden of HBV

Importantly, the lower estimate only considers costs for the minority of diagnosed patients. Factoring in the undiagnosed patients, and the costs of liver transplantation will result in costs more in line with the higher estimate. Calculations based on the data from the UK Transplant Authority suggests that transplantation for hepatitis B cirrhosis cost in the region of £7.6 million for the 152 patients transplanted between 1996 - 2000 (UK Transplant, 2002), not including the costs for post-operative follow up and chronic immuno-suppressive therapy to avoid graft rejection. That a small number of patients were transplanted is therefore conserving costs and donor livers, but careful analysis must be undertaken to monitor this future trend.

These analyses suggest that the NHS could spend between £26 million and £380 million managing hepatitis B. The total cost to the nation including time lost at work is likely to be substantially higher. These are only very rough estimates offering a broad indication of the costs. There is therefore a pressing need for a more precise estimate of the burden imposed by chronic hepatitis B on the NHS and society in general.
<table>
<thead>
<tr>
<th>Study/Country</th>
<th>Burden of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italian Ministry of Health (de Franchis et al, 2003)</td>
<td>• Annual cost of hospitalisation for CHB-related chronic liver disease: 60 million Lira (£40 million)</td>
</tr>
<tr>
<td>Harbarth 2000 - Germany</td>
<td>• Total costs related to HBV: DM 1,200 million (£589 million)</td>
</tr>
</tbody>
</table>
| Levaux 2001 - USA | • Lifetime cost per adolescent infected including asymptomatic acute infections: $4,318 (£2,350)  
• Lifetime cost per chronic infection: $64,382 (£35,030)  
(Values are in 2001 US $ and include healthcare and productivity costs). |
| Metcalf 1999 - USA | • Average cost per hospitalisation for hepatitis: $8,464 (£4,600)  
• Average cost per hospitalisation for cirrhosis: $14,063 (£7,700)  
• Average cost per liver transplant $89,076 (£49,000) |
| Veenstra 2003 - USA | • Direct medical cost of treating the 653,101 people already infected with CHB (excluding new cases): $9.4 billion (£5.1 billion) between 2002 and 2012, including 134,000 cases of cirrhosis, 41,000 cases of HCC, 6,700 liver transplants and 134,000 deaths due to CHB |
| Yang 2001 - South Korea | • Annual societal cost of HBV vaccination and disease: $957.7 million (US $1997; £520 million), with direct disease-related medical costs accounting for $632.3 million |

Table 3 Summary of studies evaluating the burden of chronic hepatitis B
Summary: Some sectors of society shoulder a disproportionate amount of the burden imposed by HBV. This chapter highlights some groups at especially high risk of contracting HBV, although all population groups are at risk to some extent. We will then explore some of the steps that healthcare professionals and the public can take to reduce the risk of becoming infected and spreading HBV.

The main route of transmission of HBV differs around the world. In the developing world, vertical transmission (from mother to child) accounts for between 40% and 50% of HBV cases and at least 95% of children born to infected mothers develop CHB (de Franchis et al, 2003; Ryder and Beckingham, 2001b).

In the UK, however, the most common routes of HBV transmission are unprotected sex and contact with blood, saliva and other bodily fluids (de Franchis et al, 2003; Lin and Kirchner, 2004). This transmission profile is similar to that of HCV and HIV, which means that many people in high-risk groups are also infected with HCV or HIV. As a result, the following groups are at increased risk of contracting HBV (Hahne et al, 2004; Ryder and Beckingham, 2001b):

- Men who have unprotected sex with men
- People who inject drugs
- People living in institutions.
- People from South Asia, Southern and Eastern Europe and Africa, who generally become infected through mother-to-baby transmission, sexual contact and medical treatment overseas

Of the estimated 7,700 new chronic hepatitis B cases per year, 96% are in the latter group of peoples who are UK immigrants. Very little is known about this group, though they are often from areas of high endemity. As the majority are in the immunotolerant phase, they may well not present to a healthcare professional until they have overt disease, whilst also being infectious. More research is urgently required to explore this contribution to the prevalence of chronic hepatitis B in the UK, and political decisions are required as to how best to manage this, via screening on entry to the UK, or in the country of origin prior to departure. Without an appropriate understanding of this problem, the UK will not have a clear understanding of the current and potential burden from chronic hepatitis B – which could have major implications for future policy.

4.1 Men who have sex with men

The Unlinked Anonymous Prevalence Monitoring Programme offers an insight into the epidemiology of HBV infection among high-risk groups. The incidence of HBV infection among homosexual and bisexual men attending genitourinary medicine clinics in England, Wales and Northern Ireland seems to have declined since the early 1990s. Nevertheless, 11% of homosexual and bisexual men born in the UK attending genitourinary medicine clinics in London in 1999 had been infected with HBV. Outside London, the prevalence was lower at 2.4%. The risk of infection rose with increased age.
The public health initiatives primarily designed to prevent HIV transmission also seem to have helped reduce the risk of HBV infection among men who have sex with men. Between 1995 and 2000, the most frequent route of HBV transmission was injecting drug use (Hahne et al, 2004). The number of men infected through unprotected sex with other men declined over this time. The number of cases following heterosexual contact proved to be stable.

Healthcare professionals offer vaccination (see section 4.5) to people at high risk of HBV infection. Uptake is, however, well below 100%. Men attending genitourinary medicine clinics were tested for antibodies to HBsAg (anti-HBs) as a marker of whether they had been vaccinated. Overall, 31% had detectable anti-HBs, with a higher prevalence of antibodies inside London than outside (40% and 24% respectively). Again, older people were more likely to be vaccinated than younger counterparts. This suggests that there is considerable scope for increasing vaccine coverage among this high-risk group.

### 4.2 Injecting drug users

Overall, 11% of injecting drug users attending genitourinary medicine clinics showed evidence of previous HBV infection. Once again, the prevalence of HBV infection was higher in London compared to other parts of the country: 16% and 7% respectively. However, more than a quarter of people injecting illicit drugs who attended specialist agencies in London in 2000 showed evidence of HBV infection. This contrasts with around one in five in the rest of the country.

Much of the risk of becoming infected with HBV seems to arise early in the career of injecting drug users. 7% of people who began injecting illicit drugs during the three years before they were assessed were infected with HBV. Prisons also seem to be an important source of infection: 25% of injecting drug users who had been in prison were infected with HBV compared with 15% of those who had not. Prisons may also provide a suitable opportunity to ensure that injecting drug users are vaccinated.

Doctors are unable to identify a route of transmission in around a third of cases. However, based on trends and the patient's age, many of these may have been infected via injecting drug use (Hahne et al, 2004). As a result, there is a need to renew efforts to engage with this difficult to reach group of patients.

### 4.3 Blood transfusions

Until relatively recently, blood transfusions and products supplied in the UK carried an appreciable risk of HBV. Increasingly rigorous screening steps helped reduce the risk of infection from blood transfusion to negligible levels. Indeed, screening means that the risk of becoming infected through blood transfusion in the UK is now less than the risk of dying during a year playing football (Allain, 2003). However, the same rigorous 'precautionary principle' is not applied in every country, which means that transfusion of blood products in some countries may carry a risk of HBV transmission.

- The main route of transmission worldwide is mother-to-baby, but in the UK it is more commonly via unprotected sex and injecting drug use
- A very significant proportion of new chronic hepatitis B cases per year are via immigration, and this is also contributing to the shift from HBeAg-positive, to HBeAg-negative disease
4. Hepatitis B: Transmission and prevention

HBV and other infections accounted for only 2% of the 1,630 serious complications of blood transfusions reported to the UK organisation Serious Hazards of Transfusion (SHOT) between 1996 and 2002 (SHOT, 2003). Of the 41 transfusion-transmitted infections occurring between 1996 and 2002, only eight involved transmission of HBV. In contrast, human errors, such as mistakes in blood sampling, labelling, delivery and infusion represent the main cause of transfusion-related morbidity and mortality in the UK, accounting for 64% of all complications reported to SHOT (Allain, 2003; SHOT, 2003).

However, there is no room for complacency, despite the indisputable success of blood screening programmes. Blood is currently screened for hepatitis B surface antigen (HBsAg). This takes between one and ten weeks to develop after exposure to HBV. As a result, there is a risk of transmission during this time. Similarly, when the patient enters the late stages of infection, HBsAg levels decline, although HBV DNA levels sometimes remain detectable. Patients who have undetectable HBsAg but detectable HBV DNA are said to have 'occult' HBV infection (Allain, 2004). The blood of such patients is capable of transmitting the infection to immunocompromised individuals, although blood containing antibodies against HBsAg does not seem to be infectious when transfused to immunocompetent recipients (Allain, 2004).

4.4 Lifestyle measures to prevent infection

People infected with HBV can take several “common sense” measures that should reduce the risk of passing the infection on to partners and other close contacts:

- Infected people should not share razors, toothbrushes or any other object that may become contaminated with blood: HBV can survive for in excess of a week in dried blood (Lin and Kirchner, 2004)
- People infected with HBV should always use an appropriate condom during penetrative and oral sex
- Any individual infected with hepatitis B should not donate blood or organs

Healthcare workers and other people likely to come into contact with body fluids should, however, assume that all patients are a potential infection risk and take appropriate precautions in addition to ensuring that they have been vaccinated.

4.5 Vaccine

A safe and effective vaccine to prevent HBV infection has been available since 1982 and more than one billion people have been vaccinated worldwide (de Franchis et al, 2003). The World Health Organisation recommends that “Routine vaccination of all infants against HBV infection should become an integral part of national immunization schedules worldwide” (World Health Organisation, 2004). At present, around 150 countries worldwide have implemented or plan to introduce universal vaccination for newborns or adolescents.
The UK, however, is one of the few countries that does not currently offer universal HBV vaccination at birth or in childhood. This reflects concerns from successive Governments that vaccination may not be cost effective due to the low reported incidence. However, a Scottish study (HepBWise) to assess the impact of HBV vaccination in 11 to 12 year old children is currently underway and a new vaccine (MF59-adjuvanted HBsAg) seems to rapidly induce an immune response that far exceeds levels recommended by the Department of Health for high-risk situations. The vaccine raises the prospect of shorter schedules, reduced need for serology and fewer boosters (Lewis et al, 2003). The results of such on-going studies may, if positive, strengthen the case for universal vaccination within the UK.

Currently, certain high-risk groups are offered vaccination, including:

- Healthcare workers
- Injecting drug users
- Individuals who frequently change sexual partners
- Infants born to mothers who have CHB
- Sexual contacts of people with CHB
- Those entering institutions or units for learning disabilities
- Renal dialysis recipients

However, as mentioned above there is considerable room to improve vaccine uptake. The number of injecting drug users who said that they had been vaccinated rose from 25% in 1998 to 35% in 2000. However, based on blood tests, only 15% of injecting drug users attending genitourinary medicine clinics had been vaccinated. In addition, only 60% of patients' sexual partners and 37% of other household members had been offered vaccination (Mangtani et al, 1998).

Less than a fifth of patients with acute hepatitis B attended a genitourinary medicine clinic before their illness, whereas 42% accessed other medical services where health care professionals could have offered vaccination (Mangtani et al, 1998). These figures suggest that the NHS needs to increase its efforts to vaccinate patients at high-risk.
Summary: Doctors diagnose hepatitis B based on a combination of symptoms and diagnostic tests. Section two summarised the hallmark symptoms of acute and chronic hepatitis B, while this section introduces some of the tests used to aid diagnosis and monitor the response to treatment.

As mentioned earlier, an antigen is a protein expressed by an invading pathogen that is capable of activating the immune system. When an antigen is identified, the immune system attacks the cells expressing the antigen. HBV has three key antigens (see also Figure 3):

- Hepatitis B core antigen (HBcAg) -- makes up the nucleocapsid that encloses HBV DNA
- Hepatitis B surface antigen (HBsAg) -- contained within the lipid envelope surrounding the nucleocapsid
- Hepatitis B "e" antigen (HBeAg) -- a non-structural protein exported from infected cells in non-viral particles while the virus is actively replicating

Measuring levels of these antigens can offer clinicians some valuable insights into the HBV infections.

5.1 Hepatitis B core antigen

There are several classes of antibodies which reflect different stages of the immune response. HBcAg can stimulate production of antibodies from two classes, known as immunoglobulin "M" (IgM) and immunoglobulin "G" (IgG):

- IgM antibodies directed against HBcAg indicate that the person was infected with HBV within the last six months
- IgG antibodies directed against HBcAg indicate that the person became infected with HBV infection more than six months previously.

Patients with CHB tend to be positive for HBsAg and IgG antibodies against HBcAg (Lin and Kirchner, 2004)

5.2 Hepatitis B surface antigen

HBsAg is detectable within the blood during acute and chronic infection. The antigen appears in the blood between one and ten weeks after exposure to HBV and persists until the infection is resolved and antibodies against HBsAg develop (Lin and Kirchner, 2004). Chronic hepatitis B is defined as the persistence of HBsAg for more than six months and many epidemiological studies use HBsAg as a marker for unresolved HBV infection. The presence of antibodies against HBsAg (anti-HBs) indicates immunity acquired through vaccination (if antibodies against HBcAg are absent) or through natural infection (if antibodies against HBcAg are present) (Lin and Kirchner, 2004).
Clinicians should assume that any patient who tests positive for HBsAg has ongoing viremia (i.e. new viral particles are being produced). For example, non-immune healthcare workers who suffer a needlestick injury involving blood from a patient positive for HBsAg should be offered prophylaxis irrespective of HBeAg status (Ganem and Prince, 2004).

5.3 Hepatitis B “e” antigen

HBeAg correlates with high levels of viral replication and a high risk of transmitting the virus. However, many people (between 50% and 80% of patients with CHB in the Mediterranean region and Southeast Asia) are infected with a mutant strain (“precore mutant”) of HBV that does not produce HBeAg (Bonino and Brunetto, 2003; Hadziyannis and Vassiliopoulos, 2001). These so-called HBeAg-negative patients can still transmit the infection, have viral DNA in their blood and have symptoms of active hepatitis. Patients infected with the HBeAg-negative mutant strain have a higher risk of progressing to cirrhosis and respond less well to interferon-alpha (de Franchis et al, 2003). The increasing prevalence of this mutant strain means that careful monitoring of HBV DNA and alanine aminotransferase levels is particularly important.

5.4 Liver function tests

People with CHB often show increased levels of liver enzymes, such as alanine aminotransferase. During flares, for example, patients may show a short-lived rise in levels of alanine aminotransferase, caused by the destruction of infected hepatocytes by the immune system (Ganem and Prince, 2004). Increases in alanine aminotransferase levels are particularly marked during acute infection, although even in chronic hepatitis, alanine aminotransferase levels are commonly two or three times higher than the upper limit of normal (Ryder and Beckingham, 2001b). Patients infected with the HBeAg-negative mutant strain of HBV are particularly prone to flares in alanine aminotransferase levels (Bonino and Brunetto, 2003).

The levels of other liver enzymes can also increase as the immune system damages hepatocytes. As a result, clinicians measure levels of several enzymes in a series of ‘liver function tests’. In many cases, patients do not develop symptoms of hepatitis despite showing markedly elevated liver enzymes. There can be a number of causes of elevated liver enzymes, such as herbal remedies, alcohol or other drugs, but they are usually a good surrogate for active liver disease.

5.5 HBV DNA levels

The most accurate and sensitive way to assess the number of viral particles (the viral load) within the body is to directly measure levels of HBV DNA within the blood. Hepatitis B virions tend to survive for only about a day or two, which means that levels of HBV DNA correlate with the current level of viral replication (Ganem and Prince, 2004; Lin and Kirchner, 2004; Ryder and Beckingham, 2001b). This makes viral load testing an effective and efficient means of monitoring treatment responses (Lin and Kirchner, 2004; Ryder and Beckingham, 2001b).
5. Diagnosis of hepatitis B

Successful treatment and an efficient immune response against the virus can both produce a marked reduction in viral load. Increased levels of HBV DNA while on treatment may indicate that the virus has developed resistance to medication – a marked problem with some antiviral drugs. However, it is also important to examine other markers of disease severity, such as liver function tests and liver biopsies, since viral load does not necessarily correlate with liver damage.

5.6 Liver biopsy

Many of the above tests (e.g. alanine aminotransferase levels) offer only an indirect measure of the extent of liver damage, which is caused by the immune response rather than the infection itself. For example, a person with a very high viral load does not necessarily have marked liver damage and vice versa. Therefore, liver biopsies offer the only way to assess directly the extent of the liver damage. During the biopsy, a thin needle is inserted into the liver under local anaesthetic and a sample is taken, which pathologists examine under a microscope.

Liver biopsies can help diagnose cirrhosis and hepatocellular carcinoma. All patients with abnormal liver function tests and detectable HBsAg need a biopsy - even if they test negative for HBV DNA or show normal liver structure on ultrasound. This is important as around one in twenty patients who present with HBsAg but no other indicators of CHB have cirrhosis (Ryder and Beckingham, 2001b).
Figure 11: Disease progression in HBeAg-positive (a) and HBeAg-negative (b) disease
6. Treating hepatitis B

Summary: Despite a lack of awareness among researchers and physicians, a growing number of treatments are now available that can improve the prospects for people with hepatitis B. This chapter introduces the mainstays of management for hepatitis B and looks at some of the prospects for future hepatitis B treatments.

6.1 Acute hepatitis B

Acute hepatitis B is usually a self-limiting disease that does not need treatment other than symptomatic relief. In a very small number of patients, acute hepatitis B can result in acute liver failure (“fulminant hepatitis”). This rare occurrence can be fatal or require liver transplantation (Ryder and Beckingham, 2001a).

However, acute hepatitis B can be prevented through prophylactic vaccination or administration of hepatitis B immunoglobulin (antibodies against the virus). People known to have been exposed to the infection – for example, healthcare workers who suffer a needlestick injury involving blood that could contain HBV should receive hepatitis B immunoglobulin, if they are not already vaccinated or did not respond to previous vaccination.

6.2 Treatments for chronic hepatitis B

Treatment of CHB aims to prevent the progression to hepatocellular cancer and cirrhosis. A growing number of therapeutic options allow clinicians to improve the prognosis of people with CHB.

6.2.1 Interferon-alpha

Until recently, Interferon-alpha was the mainstay of CHB management. Interferon-alpha is a genetically engineered (“recombinant”) version of a protein naturally produced by immune cells in response to viral infections. Interferon-alpha acts in two ways: to reduce viral replication and to increase levels of cytokines (inflammatory mediators) involved in the body’s response to infection (Lin and Kirchner, 2004). In this way, Interferon-alpha activates the immune system, increasing the proportion of HBeAg positive patients who undergo HBeAg seroconversion (Craxi et al, 2003).

However, treatment is given as three injections of Interferon-alpha each week for between four and six months, which can be inconvenient for patients. In addition, Interferon-alpha stops viral replication in only around 40% of patients and very few patients lose HBsAg. Nevertheless, liver biopsies usually show a sustained improvement and patients are less likely to develop end-stage liver disease and, possibly, hepatocellular cancer (Ryder and Beckingham, 2001b).
Side effects are the major limitation of treatment with Interferon-alpha. Around 15% of patients are unable to tolerate treatment due to side-effects (Ryder and Beckingham, 2001b). These side-effects include:

- loss of appetite
- nausea
- influenza-like symptoms
- lethargy
- depression
- cardiovascular problems, such as high/low blood pressure or an irregular heartbeat (British Medical Association, September 2004)

Many patients treated with Interferon-alpha experience flares of high aminotransferase levels before or during HBeAg seroconversion. These flares arise from increased immune activity and, as such, often indicate that the body is attempting to clear the infection. In decompensated cirrhosis, flares can precipitate liver failure, which may require liver transplantation. As a result, Interferon-alpha, unlike the antiviral drugs mentioned below, are contra-indicated in patients with decompensated cirrhosis (Ganem and Prince, 2004).

6.2.2 Lamivudine

Lamivudine is a nucleoside analogue, which means it mimics one of the bases that make up the genetic code. The DNA polymerase enzyme that constructs the HBV DNA molecule within the new viral particles mistakes Lamivudine for a normal base and therefore incorporates it into the DNA molecule blocking replication. As a result, Lamivudine potently inhibits production of new viral particles (Lin and Kirchner, 2004; Ryder and Beckingham, 2001b).

By blocking viral replication, Lamivudine reduces inflammation, prevents liver damage and slows disease progression (Lai et al, 1998). Clinical trials have shown that Lamivudine is effective and well tolerated during sustained therapy lasting three years (Yao et al, 2004). Nevertheless, around 26% of patients develop resistance to Lamivudine each year, with up to 80% of patients becoming resistant after five years of treatment (Lai et al, 2003; Lok et al, 2003). Lamivudine resistance arises due to mutations changing the shape of the DNA polymerase enzyme. One such mutation is termed "YMDD" after the building blocks (amino acids) that are changed within the protein. Clinicians can suspect the emergence of resistant strains by monitoring levels of HBV DNA and alanine aminotransferase regularly, and confirm the mutations by sequencing the viral DNA, and considering alternative treatments if levels rise. Such patients need treatment with alternative therapies.

- Acute hepatitis B usually only requires symptomatic relief, but infrequently can result in fulminant hepatitis, which can require liver transplantation, or be fatal
- Treatments for chronic hepatitis B have utilised interferon-alpha, lamivudine and more recently adefovir dipivoxil
6.2.3 Adefovir dipivoxil

Adefovir dipivoxil (Hepsera) is a new therapy, which became available in the UK in April 2003. Adefovir is a nucleotide analogue and resembles one of the natural bases that make up DNA even more closely than Lamivudine (Dusheiko, 2003). Clinical trials have found that Adefovir is a tolerable and effective therapy for CHB, improving liver histology, reducing viral load and normalising alanine aminotransferase levels to a similar extent to Lamivudine (Hadziyannis et al, 2003; Marcellin et al, 2003). Like Lamivudine, Adefovir is effective in patients infected with the HBeAg-negative mutant strain of HBV (Hadziyannis et al, 2003).

These benefits seem to be sustained during long-term treatment. Several recent studies suggest that three years treatment with Adefovir dipivoxil produces significant and sustained reductions in viral load and alanine aminotransferase levels (Benhamou et al, 2004; Hadziyannis et al, 2004). The proportion of patients with undetectable HBV DNA and normal levels of alanine aminotransferase also increased over the duration of therapy.

Resistance to Adefovir appears to be comparatively rare. In clinical trials, only 3.9% of patients developed resistance after three years of treatment (Qi et al, 2004), compared with more than 50% of those receiving Lamivudine (Lai et al, 2003; Lok et al, 2003). Mutant strains of HBV that are resistant to Adefovir seem to remain susceptible to Lamivudine (Qi et al, 2004), while several clinical trials have shown that Adefovir is highly effective against Lamivudine-resistant strains of HBV (Perrillo et al, 2004; Peters et al, 2004; Schiff et al, 2003).

6.2.4 Future medications for CHB

Several other antiviral therapies are being investigated or developed for CHB (de Franchis et al, 2003), for example:

- Pegylated Interferon-alpha is a modified version of Interferon-alpha, with a polyethylene glycol (PEG) molecule attached to slow excretion and alter the distribution of Interferon-alpha in the body (also resulting in once a week administration). Pegylated Interferon-alpha 2a is currently in phase III trials for chronic hepatitis B, having been licensed for chronic hepatitis C in 2002.
- Entecavir and Telbivudine are nucleoside analogues in clinical trials for CHB. Unlike Lamivudine, they selectively inhibit HBV DNA polymerase and are relatively inactive against HIV, which could be an advantage for these new therapies.
- Tenofovir is another nucleotide analogue, which is currently licensed for HIV, and has been investigated by some centres.

Tenofovir, Entecavir and Telbivudine, like Adefovir seem to be active against Lamivudine-resistant HBV (Ganem and Prince, 2004).
Given the increasing array of effective medicines, combination therapy will probably become the treatment of choice for CHB to minimise the risk of drug resistance and ensure durable efficacy. However, the ideal combination and duration of treatment remains unresolved. Furthermore, the risk of cross-resistance is not fully characterised (Ganem and Prince, 2004).

6.3 Liver transplantation

Around 600 to 700 liver transplants are conducted in the UK each year. Around 5.5% of these are for people with HBV-associated liver damage (de Franchis et al, 2003). Liver transplantation is an expensive procedure: the operation alone costs £18,370 (Department of Health, 2004) and transplant recipients also require a range of expensive medication and outpatient consultations before and afterwards. In addition to the monetary cost of this operation, there are only a limited number of organs suitable for transplantation. This means that every transplant given to someone with chronic hepatitis B is one organ that cannot be given to save the life of another patient. This makes prevention of HBV transmission and treatment to prevent disease progression all the more important.

Patients who undergo liver transplantation require potent immunosuppressant drugs to prevent the body from rejecting the new organ. The suppression of the immune system means that patients are at risk of a recurrence of CHB and that recurrent infections are associated with high viral loads and poor outcomes. Without treatment to prevent disease recurrence, more than 80% of patients who receive a liver transplant will experience reinfection (Ganem and Prince, 2004). However, treating CHB patients with hepatitis B immunoglobulin and antivirals such as lamivudine and adefovir dramatically improves prognosis following a transplant (Ganem and Prince, 2004; Naoumov et al, 2001).
Summary: The management of hepatitis B poses particular problems in certain patient groups such as pregnant women and people with HIV. However, as these examples show, researchers are making marked progress tackling these issues.

7.1 Pregnancy

At least 95% of children born to infected mothers develop CHB unless they receive hepatitis B immunoglobulin and/or prophylactic vaccination soon after birth (Ryder and Beckingham, 2001b). To reduce the risk of vertical transmission from mothers to children, the Department of Health advised in April 2000 that all pregnant women should be screened for HBsAg (Department of Health and Royal College of Midwives, 2000). If further tests confirm a positive initial result, the mother is tested for HBeAg. Babies born to women who test positive for HBsAg should be immunised with hepatitis B vaccine. The baby should also receive hepatitis B immunoglobulin if the mother is positive for HBeAg or suffers acute HBV infection during pregnancy. Vaccination and, if appropriate, administration of immunoglobulins should take place, ideally, as soon as possible. However, of all children should be treated within 24 hours of birth. The child will need additional doses of vaccine at one, two and 12 months of age. Such vaccination prevents transmission in more than 90% of cases (de Franchis et al, 2003). Provided that a baby born to a mother infected with HBV receives the first dose of vaccine at birth and completes the course, the baby can be breast fed (Department of Health and Royal College of Midwives, 2000).

The Department of Health has also published information leaflets for pregnant women who test positive for HBV during antenatal screening (Department of Health, 2002b). The leaflet provides information about hepatitis B and the implications for the baby, the mother and close contacts. This leaflet emphasises the importance of completing the course of immunisation to protect the baby.

Prophylactic vaccination of newborns is especially important since 95% would otherwise develop CHB (Ryder and Beckingham, 2001b), which would have a substantial impact on health and NHS resources. Studies suggest that current approaches to prevent vertical transmission seem to be working. For example, Hesketh and colleagues examined 2,025 serum specimens collected from children aged 13-14 years (Hesketh et al, 1997). Six specimens showed evidence of resolved infection, one specimen showed evidence of recent infection, while three contained HBsAg. The carriage rate (0.15%) was consistent with the vertical transmission before antenatal screening and neonatal vaccination. By adolescence, about one in 200 children has been infected with HBV. Among people of South Asian descent, infections acquired in childhood are more common than among the population as a whole (Hahne et al, 2003). Universal immunisation against HBV would not reduce childhood infection levels any more than the current policy (Hesketh et al, 1997), but it would prevent infections in adolescence and later life.
7.2 Co-infection with Human Immunodeficiency Virus

As mentioned elsewhere, HBV and HIV share several risk factors and routes of transmission (Hyun and Coyle, 2004). As a result, between 64% and 84% of people with HIV have antibodies against HBcAg (indicating past or present infection) and 16% of people with HIV also suffer from CHB (Hyun and Coyle, 2004). People with HIV are 10 times more likely than the general population to be positive for HBsAg (Benhamou, 2004).

Highly active antiretroviral therapy (HAART) markedly reduces HIV-related deaths. As a result, morbidity and mortality from conditions unrelated to HIV are increasing among people living with HIV (Hyun and Coyle). Indeed, end-stage liver disease is now a common cause of morbidity and mortality among people with HIV (Thio, 2004).

Concurrent HIV infection alters the natural history of hepatitis B. In people infected with both viruses, liver disease is more severe with a higher risk of cirrhosis and patients have reduced expression of HBeAg and higher viral load than in people with hepatitis B alone (de Franchis et al, 2003; Dervisevic and Pillay, 2003; Thio, 2004). The presence of HBsAg also seems to be associated with an increased risk of hepatotoxicity among patients taking HAART (Benhamou, 2004).

Fortunately, standard treatment options remain effective in people with HIV. Lamivudine and Adefovir, for example, inhibit HBV replication in people with concurrent HIV (Benhamou, 2004; Benhamou et al, 2001) and Lamivudine is also licensed for the treatment of HIV in combination with other medications. Tenofovir also appears to be effective against HBV as well as HIV, although it is not currently licensed for CHB. However, Lamivudine and Tenofovir should not be given to patients with HIV who are not also receiving a HAART regimen due to the risk of HIV developing drug resistance (de Franchis et al, 2003; Keeffe et al, 2004).

Against this background, consensus guidelines suggest that clinicians should assess whether the patient’s HIV infection requires a HAART regimen (de Franchis et al, 2003; Keeffe et al, 2004). Patients receiving or needing HAART can be given Adefovir, Lamivudine or Tenofovir in addition to other drugs active against HIV. Those who need treatment for CHB but not HIV infection can be given Adefovir.

- At least 95% of children born to mothers with chronic hepatitis B also develop infection, unless they receive hepatitis B immunoglobulin and vaccination
- 16% of HIV-positive people have chronic hepatitis B as well, and coinfection can result in an increased risk of hepatotoxicity, morbidity and mortality, requiring careful selection of antiviral drugs against both HIV and hepatitis B.
Summary: The preceding chapters highlighted the heavy clinical and economic burden that hepatitis B places on the NHS, with both acute and chronic hepatitis B causing considerable mortality and morbidity. This chapter examines the extent to which current service provision and commissioning arrangements meet the needs of people infected with HBV.

The current NHS infrastructure does not allow commissioning bodies to meet the needs of people with hepatitis B. The National Specialist Commissioning Advisory Group (NSCAG), is the only specialist service commissioning for liver services, but it only covers liver transplantation.

A recent survey of 41 specialists from 33 NHS Trusts found that service demand, provision and treatment varied widely. For example, 17 of those who responded treated only between 10% and 20% of patients with CHB. In contrast, 11 centres treated between 40% and 60% of their patients, while one tertiary centre treated more than 80%. This variation may reflect differences in the patient population or differences of opinion surrounding the criteria for treating patients. The survey revealed that there is currently no audit of HBV patient numbers in the UK, which makes it almost impossible to accurately assess the burden of this disease. Typically, however, a District General Hospital sees between two and three new patients per month, whereas a main centre may see between 10 and 15 new patients per month.

Patients with hepatitis B and other forms of viral hepatitis are treated by a range of specialists, including hepatologists, gastroenterologists and infectious disease specialists. However, there is no formal training for hepatologists in the UK, despite their being a proposal for an accredited sub-specialty of Gastroenterology from the Specialist Advisory Committees. This was rejected by the Government because of the policy to shorten rather than lengthen postgraduate specialist training. While primary care staff may monitor patients, they often have little experience and expertise in managing liver disease. There is therefore a need for more training of primary care staff, particularly for those serving communities who have an especially high prevalence of chronic hepatitis B.

Against this background, commissioning liver services can be complicated. For example, the survey found that referrals for chronic hepatitis B can come from:

- GP screening (e.g. abnormal liver function tests)
- Occupational Health screening
- Drug services
- Alcohol services
- Sexual Health services
- Prisoner populations
- Screening of patient families
- Screening high risk ethnic groups e.g. Southeast Asian
Furthermore, liver disease is heterogeneous and may not produce a consistent health burden over time. The impact of the disease falls on a variety of NHS departments, society more widely and government policy ranging from ‘mainstream’ health services, to services for substance misuse and alcoholism. Specialised services for chronic hepatitis B will cross commissioning boundaries. As a result, Primary Care Trusts will need to amalgamate their commissioning processes to address this, possibly via a nominated lead Primary Care Trust for liver disease, with oversight from Strategic Health Authorities (SHAs) and Regional Specialised Commissioning Groups (RSCGs).

Whatever the particular structure, commissioners of liver services require statutory powers with devolved budgets for liver disease generally and hepatitis B in particular. At present, hepatitis C costs often overshadow those of hepatitis B, although the diseases are often managed from the same budget. Therefore specialist treatment budgets for chronic hepatitis B should be allocated.

Commissioners should ensure that specialised service commissioning is implemented, monitored and evaluated via managed clinical networks. Local protocols should be drawn up to help clinicians select patients for treatment. Extra funding may be needed to ensure that suitable patients can be treated with antiviral drugs. All patients should be monitored during treatment for response (based on the decrease in viral load), side effects and the emergence of resistant strains. The service should also collect data on patients with viral hepatitis, monitor outcomes in treated and untreated patients as well as screening patients to detect liver cancer early. This structure would also facilitate enrolment into clinical trials. As a result, the Foundation for Liver Research believes that there should be an urgent review of commissioning specialised liver disease services.

- A recent survey of 41 specialists in 33 NHS Trusts illustrates the variation in service demand, provision and treatment rates
- Patients with chronic hepatitis B see a wide range of specialists, such as hepatologists, gastroenterologists and infectious disease physicians
- Formal training recognition of Hepatology has been rejected by the Government, and there is also a need to ensure appropriate training of primary care staff
- Specialised commissioning of NHS services need to reflect the heterogeneity of chronic hepatitis B, via a nominated lead Primary Care Trust, with oversight from Strategic Health Authorities and Regional Specialised Commissioning Groups
The Foundation for Liver Research believes the following areas are in need of urgent review and funding:

1. **Raise the priority of chronic hepatitis B**

Government, policymakers, purchasers, service providers and physicians must recognise the dangers of chronic hepatitis B as a public health problem, as well as the dangers of ignoring it. Without doing this, little action will follow and our recommendations will not be heeded.

2. **Research**

   - **Improve epidemiological research**
     The UK must invest in and perform epidemiological research on the true incidence and prevalence of chronic hepatitis B, and in particular into the demographic shift in populations affected; HBeAg negative disease; the uncertainty surrounding immigration and the rise in prevalence of chronic hepatitis B; and the risk to the wider community in the immediate future.
   
   - **Invest in basic research.**
     Chronic hepatitis B does not attract the same level of research funding as many other diseases, which impose a lower burden nationally. It is essential more research is conducted into the pathogenesis and treatment of this important public health threat.
   
   - **Determine the economic burden**
     Estimates suggest that the NHS currently spends up to £26 million managing chronic hepatitis B in diagnosed patients. The total cost for all patients, including time lost at work, could reach £429 million. These are only very rough estimates and there is a pressing need for a more rigorous estimate of the economic burden imposed by chronic hepatitis B on the NHS and society more generally.

3. **Improving service provision**

   - **Evaluate and understand the needs of people living with CHB**
     We call for policy makers, purchasers, service providers, and physicians to ensure that the needs of people living with hepatitis B are investigated fully, that social and healthcare services meet those needs and that there is equitable access to services.
   
   - **Develop managed clinical networks for viral hepatitis**
     This model of NHS configuration is, we believe, the basis for effective service provision, which requires hepatology, gastroenterology, infectious disease services, genitourinary medicine, hepatitis nurses, diagnostics, and primary care to work together to deliver services efficiently via locally agreed strategies, with appropriate resources for education and audit.
4. Prevention

• Improve vaccine coverage
  The Foundation for Liver Research strongly recommends that the Department of Health introduce universal HBV vaccination alongside a well resourced selective vaccination programme as a matter of urgency.

• Improve awareness
  The Government, the media, charities and healthcare workers need to increase awareness of HBV across the whole population, and in particular those communities most at risk. We hope that this report goes some way to meeting this need and ensuring that chronic hepatitis B moves out from the shadows.


Peters, M.G., Hann Hw, H., Martin, P., Heathcote, E.J., Buggisch, P., Rubin, R., Bourliere, M., Kowdle, K., Trepo, C., Gray Df, D., Sullivan, M., Kleber, K., Ebrahim, R., Xiong, S. and...


UK Transplant. (2002) Statistics prepared by UK Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland.


11. Glossary

**Acute hepatitis B**: infection with hepatitis B for less than six months

**Alanine aminotransferase**: an enzyme produced in liver cells that leaks out into the blood when liver damage occurs.

**Antigen**: a foreign substance that can trigger an immune system response, resulting in production of an antibody as part of the body’s defence against disease.

**Anti-HBs**: antibody to the hepatitis B surface antigen.

**Ascites**: An accumulation of serous fluid in the peritoneal cavity, often due to liver dysfunction.

**cccDNA**: covalently closed circular DNA, which is an intermediary used during the replication of hepatitis B.

**Chronic hepatitis B**: infection with hepatitis B for greater than six months

**Cirrhosis**: a serious liver condition characterized by scarring of the liver that can lead to liver failure and death. Continuous inflammation of the liver, which can lead to excess scar formation or fibrosis. Scarring results in the loss of liver cells and impairs liver function.

**Compensated cirrhosis**: Cirrhosis is scarring of the liver that involves the formation of fibrous (scar) tissue associated with the destruction of the normal architecture of the organ, but is compensated when residual function of the liver is preserved.

**Cytokines**: chemical messengers that are involved in the regulation of almost every system in the body and are important in controlling local and systemic inflammatory response.

**Cytopathic**: of, relating to, characterized by, or producing pathological changes in cells (e.g. cell death).

**Cytoplasm**: the living matter within a cell (excluding the nucleus) that is responsible for the function of the cell (for example, protein synthesis).

**Dane Particle**: the complete hepatitis B virion.

**Decompensated cirrhosis**: Cirrhosis is scarring of the liver that involves the formation of fibrous (scar) tissue associated with the destruction of the normal architecture of the organ, but is decompensated when the liver fails following loss of any residual function of the liver.

**DNA polymerase**: an enzyme that creates new DNA strands using DNA templates during replication.

**Fibrosis**: refers to the presence of scar tissue or collagen fibres in any tissue. In the liver, fibrosis or scarring of the liver damages the architecture and thus the functionality of the organ. Fibrosis, combined with the liver’s ability to regenerate, causes cirrhosis (regeneration within the scar tissue).

**Fulminant hepatitis**: acute liver failure

**HBeAg negative disease**: chronic hepatitis B infection characterised by the absence of hepatitis B e antigen, but with the presence of liver disease (e.g. inflammation and fibrosis), often due to a mutation in the hepatitis B virus.

**HBeAg positive disease**: chronic hepatitis B infection characterised by the presence of hepatitis B e antigen and liver disease (e.g. inflammation and fibrosis).

**Hepatitis B Core Antigen (HBcAg)**: the structural viral proteins that make up the nucleocapsid that encloses the hepatitis B DNA.

**Hepatitis B e Antigen (HBeAg)**: the non-structural viral protein exported from infected cells in non-viral proteins while hepatitis B is actively replicating.

**Hepatitis B Surface Antigen (HBsAg)**: the structural viral proteins contained within the lipid envelope surrounding the nucleocapsid.

**Hepatitis**: inflammation of the liver.

**Hepatocellular carcinoma**: a malignant tumour of the liver (“primary liver cancer”). Chronic hepatitis B and C infections may increase the risk of developing liver cancer.

**Hepatocyte**: a liver cell

**Hepatotoxicity**: a general term for liver damage, often caused by drug therapy.

**Icteric**: pertaining to jaundice.

**Immunoglobulin**: a general term for antibodies, which bind to invading organisms, leading to their destruction. There are five classes of immunoglobulins: IgA, IgG, IgM, IgD and IgE.

**Immuno-suppressive therapy**: treatment to selectively suppress the immune system in order that a donor organ is not rejected after transplantation.

**Immunotolerant phase**: the initial stage of chronic infection when serum hepatitis B surface antigen and hepatitis B e antigen are detectable; serum HBV-DNA levels are high; and such enzymes as the alanine aminotransferase are normal or minimally elevated.
Incidence: the number of new cases of a diseases or condition in a specific population over a given period of time.

Inflammation: the body’s response to tissue injury or infection, which typically includes increased vessel dilation and permeability, and is characterised by an immune response and migration of white blood cells to the affected area.

Interferons: cytokines belonging to a family of antiviral proteins that occur naturally in the body that help the immune system function in a number of ways.

Jaundice: Yellowish discoloration of all the tissues in the body, including the white of the eyes and the skin, which occurs when the blood contains abnormal amounts of the pigment bilirubin, which is normally excreted in the bile.

Liver function test: a simple blood test that provides information on the function of the liver, possible abnormalities and causes.

Managed clinical networks: the arrangement of NHS clinical services to bring together patients and health professionals from all disciplines to plan services locally, based on local needs and priorities, but to nationally agreed standards.

Messenger RNA: The RNA molecule that contains the coded information for the amino acid sequence of a protein.

National Specialist Commissioning Advisory Group (NSCAG): the body that advises the Secretary of State for Health on very specialised services, which need to be provided in a small number of centres, and planned and funded on a national basis.

Necrosis: death of cells in a tissue or organ caused by disease or injury.

Nucleocapsid: the nucleic acid and its surrounding protein coat or capsid; the basic unit of virion structure.

Nucleoside analogue: Any of a group of antiviral drugs, such as Lamivudine, that interfere with the activity of the viral enzyme reverse transcriptase and are used in the treatment of HIV or chronic hepatitis B.

Nucleotide analogue: Any of a group of antiviral drugs, such as Adefovir dipivoxil, that interfere with the activity of the viral enzyme reverse transcriptase and are used in the treatment of HIV or chronic hepatitis B.

Precore mutant: a form of hepatitis B virus that does not produce the hepatitis B e antigen.

Pre-genomic RNA: this is packaged with the various enzymes into core particles which serve as a template for reverse transcription during the replication of hepatitis B.

Prevalence: the total number of cases of a particular disease at a given moment in time, in a given population.

Primary Care Trust (PCT): an NHS trust that provides all local GP, community and primary care services and commission hospital services from other NHS trusts. They are managed by a Board elected from local GPs, community nurses, lay members, the Health Authority and Social Services.

Regional Specialised Commissioning Group (RSCG): These bodies are groups of NHS commissioners (previously health authorities and now Primary Care Trusts) whose boundaries are currently based on the former eight Regional boundaries in England, responsible for overseeing specialised services commissioning.

Revers transcripion: the copying of an RNA molecule back into its DNA complement. The enzymes that perform this function are called reverse transcriptases.

Selective vaccination: active vaccination of individuals or communities most at risk in a population due to certain behaviours or lifestyles.

Seroconversion: the development of antibodies against a microorganism; the change in a person’s antibody status from negative to positive.

Strategic Health Authority (SHA): The whole of England is split into 28 Strategic Health Authorities (SHAs). These organisations were set up in 2002 to develop plans for improving health services in their local area and to make sure their local NHS organisations were performing well.

Universal vaccination: active vaccination of a population, often following birth in early adolescence.

Vertical transmission: transmission from a mother to a foetus or newborn. Vertical transmission may occur in utero (in the womb), intrapartum (during birth) or postpartum (via breast-feeding).

Viral load: the amount of virus present in a person’s blood stream. It is usually measured by the PCR quantitative test and the result is given in the number of virus particles per millilitre of blood. It may sometimes be written as viral titre.

Virion: a complete virus particle that exists outside of a host cell.

YMDD mutation: the change in the hepatitis B genome that confers resistance to the drug Lamivudine.

List of abbreviations

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<tr>
<td>CHB</td>
<td>Chronic hepatitis B</td>
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<tr>
<td>EASL</td>
<td>European Association for the Study of the Liver</td>
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<td>ELDIT</td>
<td>Epidemiology of Liver Disease in Tayside</td>
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<tr>
<td>HAART</td>
<td>Highly-active anti-retroviral therapy (a combination of drugs used to treat HIV)</td>
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<td>HBCAg</td>
<td>Hepatitis B &quot;c&quot; (core) antigen</td>
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<td>HBeAg</td>
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<td>HBSAg</td>
<td>Hepatitis B &quot;s&quot; (surface) antigen</td>
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<td>HCC</td>
<td>Hepatocellular carcinoma</td>
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<td>HGV</td>
<td>Hepatitis G virus</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>MRSA</td>
<td>Methicillin Resistant Staphlococcus Aureus</td>
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<td>PCT</td>
<td>Primary Care Trust</td>
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<td>SARS</td>
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