

National Cancer Prevention Policy

2007–09



Immunisation

Hepatitis B

H e p a t i t i s B

Introduction

At least 25% of those with chronic hepatitis B infection will develop hepatocellular cancer

The hepatitis B virus (also known as HBV) was discovered in the 1960s; however, chronic hepatitis B infection (also known as CHB) was suspected as a cause of liver cancer from the early 1940s (Heymann 2004).

Hepatitis B is a hepadnavirus that contains partially double-stranded DNA (Heymann 2004). The outer surface of the virus contains the hepatitis B surface antigen (HBsAg). Other important antigenic components are the hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). These antigenic components form the foundation of serological diagnosis of hepatitis B infection and immunity (Heymann 2004).

Hepatitis B replicates almost exclusively in the liver but very high concentrations of virus are released into the blood, so that most tissues and body fluids are infectious. Transmission occurs through percutaneous or mucous membrane contact with infected blood or body fluids. This can occur by needle/syringe sharing, sexual intercourse and even in household settings, possibly through the use of shared objects, such as razor blades, where infectious virus has been shown to persist for up to a week (Lavanchy 2004; Previsani, Lavanchy & Zuckerman 2004; Tawk et al. 2006a). The major mode of transmission on a global level is from mother to child, around the time of birth. If a pregnant woman has active or chronic hepatitis B infection and presence of HBeAg (indicating higher levels of hepatitis B viral load), the risk of infection in her newborn infant is 90% (Previsani, Lavanchy & Zuckerman 2004). During much of the last century, blood transfusions were a potential source of hepatitis B but the Australian Red Cross Blood Service has routinely screened all donated blood products and organ donors for a number of viruses, including hepatitis B, which has been screened for since 1975.

Hepatitis B infection causes symptomatic acute hepatitis in approximately 30% to 50% of adults, but in young children, particularly those aged less than one year, infection is usually asymptomatic (Heymann 2004). The incubation period is 45 to 180 days and the period of communicability extends from several weeks before the onset of acute illness usually to the end of the period of acute illness.

Acute illness is indistinguishable from other forms of hepatitis and symptoms include fever, jaundice, malaise, anorexia, nausea and vomiting, abdominal pain, myalgia and the passage of dark-coloured urine and light-coloured stools. During recovery, malaise and fatigue may persist for many weeks. Fulminant hepatitis, which occurs in approximately 1% of cases, is a clinical syndrome of sudden onset occurring in people without pre-existing liver disease, and results in severe impairment of liver function, sometimes with cerebral oedema and encephalopathy.

Chronic hepatitis B infection occurs when the immune response fails to clear acute infection. Markers of chronic hepatitis B infection are the persistence of HBsAg, with or without HBeAg, for more than six months after initial infection. This is further determined by the presence of hepatitis B DNA. Chronic infection occurs in 1% to 5% of adults, but is more common in immunocompromised persons and considerably more common in infants infected around the time of birth (up to 90%) (Heymann 2004; Lavanchy 2004; Ocama, Opio & Lee 2005; Previsani, Lavanchy & Zuckerman 2004). People with chronic hepatitis B infection, particularly those who are HBeAg positive, can transmit hepatitis B to others via the routes discussed above.

The complications of chronic hepatitis B infection include progression to cirrhosis in up to 30% of cases (Fattovich et al. 2004; Villeneuve 2005). Cirrhosis is a serious liver disease associated with chronic and often widespread destruction of liver substance occurring over a period of several years. Because liver inflammation can be totally symptomless, progression of inflammation to cirrhosis can occur without the knowledge of the patient. Chronic hepatitis B infection is the major cause of hepatocellular carcinoma (HCC) worldwide (Lavanchy 2005; WHO 2004).

Australia

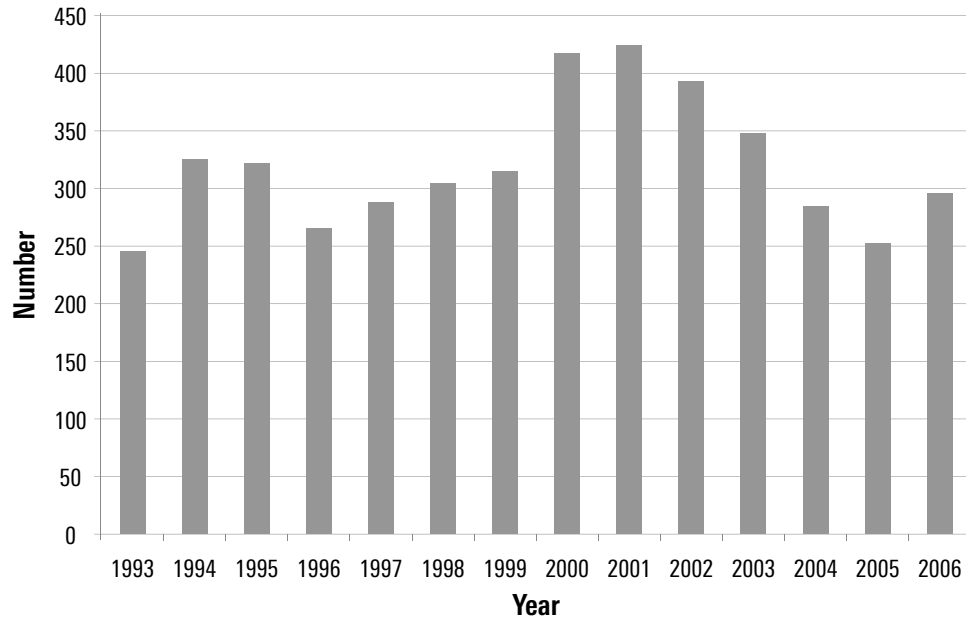
Hepatitis B infection is a notifiable condition in Australia. There are two case definitions applied to notifications of hepatitis B: incident and unspecified.

- **Incident hepatitis B** is recorded when there is no evidence of hepatitis B infection in the past 24 months and serological markers such as HBsAg and IgM core antigen are present or hepatitis B DNA and IgM core antibodies are present. In 2005, 245 cases of incident hepatitis B were reported to the National Notifiable Diseases Surveillance System (NNDSS 2007). Of the people with incident hepatitis B notified in 2005, 46% reported injecting drug use exposure and 34% reported sexual exposure (NNDSS 2007).
- **Unspecified hepatitis B**, defined where a person does not meet the criteria for a newly acquired hepatitis B infection but has laboratory evidence of hepatitis B infection, accounted for 6396 notifications in 2005 (NNDSS 2007).

The Northern Territory has the highest reported rates of incident and unspecified notifications of hepatitis B; chronic hepatitis B infection is considered endemic in Aboriginal and Torres Strait Islander communities. Studies undertaken in the mid-1990s indicated that up to 25% of rural Aboriginal populations were HBsAg positive (Fisher & Huffam 2003; O'Sullivan et al. 2004; Wood et al. 2005). A large proportion of chronic hepatitis B infection cases occur among people born in Asia and the Pacific Islands and also among people born in other hepatitis B-endemic areas such as the Middle East, Mediterranean and central or northern Africa (O'Sullivan et al. 2004; Tawk et al. 2006a), with the vast majority of these cases presumed to have been acquired overseas. In addition, Australian and overseas-born children of parents from these hepatitis B endemic regions, who were born prior to the introduction of the universal infant hepatitis B vaccination program in Australia, are at an increased risk of acquiring hepatitis B, either perinatally or through horizontal transmission.

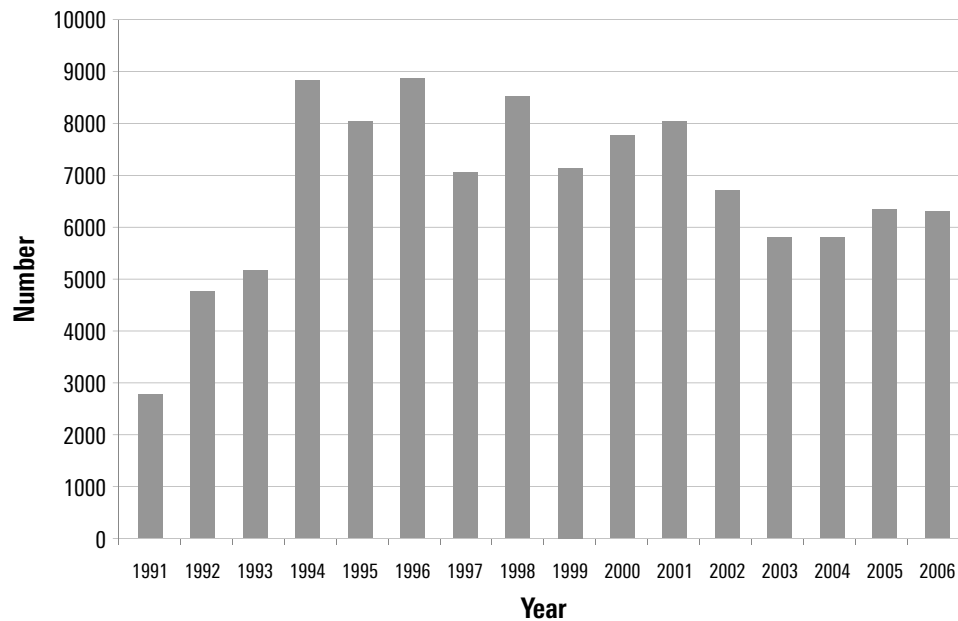
Figure 3.1 shows the number of incident hepatitis B notifications from 1993 to 2006 (mean notifications per year = 315) and Figure 3.2 shows the number of unspecified notifications from 1991 to 2006, total over 90,000 notifications during those 15 years (NNDSS 2007).

Figure 3.1 Incident hepatitis B notifications 1993–2006



Source: NNDSS 2007

Figure 3.2 Unspecified hepatitis B notifications, 1991–2006



Source: NNDSS 2007

Global

Globally, an estimated two to three billion people have been infected with hepatitis B and of these, more than 400 million suffer from chronic hepatitis B infection (Goldstein et al. 2005; Lavanchy 2004; Lavanchy 2005; WHO 2004). At least 25% of those with chronic hepatitis B infection will develop hepatocellular cancer (HCC), making HCC the tenth leading cause of death worldwide (Ghany & Doo 2004; Lavanchy 2004; Lavanchy 2005; Previsani, Lavanchy & Zuckerman 2004).

Over 75% of people with chronic hepatitis B infection reside in the Asia-Pacific region (Lesmana et al. 2006). Within this region is the Western Pacific Region, which consists of 37 countries, including Australia (WHO 2004). Australia, New Zealand and Japan are all considered low prevalence countries (Clements et al. 2006; Lesmana et al. 2006). In the Western Pacific Region, hepatitis B seroprevalence estimates range from less than 1% to 20%. China has the highest prevalence and accounts for more than a third of the global burden of chronic hepatitis B infection. Vietnam, Taiwan and the Philippines also report hepatitis B seroprevalence rates of up to 20% (Clements et al. 2006; Lesmana et al. 2006). There are approximately 280,000 deaths in the Western Pacific Region each year attributable to complications arising from hepatitis B infection. Over 90% of these deaths are due to hepatitis B acquired decades earlier at birth or during childhood (Clements et al. 2006). Hepatitis B vaccination has been introduced into the Western Pacific Region to improve hepatitis B control in this region.

The link between hepatitis B infection and cancer

An association between chronic liver damage from any cause and hepatocellular carcinoma (HCC) was well known before the discovery of hepatitis B (Kew 2002). It was obvious that countries with very high chronic infectious hepatitis rates were also among those with the highest prevalence of HCC (Bosch & Ribes 2002). The introduction of serologic tests for hepatitis B in the late 1960s further supported the connection between chronic hepatitis B infection and HCC. In 1994 hepatitis B was classified as a carcinogen by the International Agency for Research on Cancer (IARC 1997). Case-control studies from various regions of the world have consistently demonstrated that chronic hepatitis B infection is more common among HCC cases than controls (IARC 1997). A number of studies have demonstrated the geographic coincidence between hepatitis B endemicity and HCC prevalence (Beasley et al. 1981; Chan et al. 2004; Craxi & Camma 2005; Heymann 2004; Lee, Hsieh & Ko 2003; Lok 2004).

Multiple factors appear to play a role in the progression of chronic hepatitis B infection to HCC, with chronic inflammation and cytokine effect playing a major role in the development of fibrosis and ongoing hepatocyte generation. Hepatitis B DNA has also been demonstrated to be integrated into cellular DNA in samples of HCC (Brechot 2004; Chang et al. 2005; Hayashi & Di Bisceglie 2005). Various other viral factors associated with HCC development include the hepatitis B genotype, viral mutations and high viral load (Brechot 2004; Chan et al. 2004; Chen et al. 2006; McGlynn & London 2005; Tang et al. 2004; Yu et al. 2005). The direct involvement of the hepatitis B virus in carcinogenesis has now been shown to be related to expression of several hepatitis B proteins (Bonilla & Roberts 2005; Brechot 2004). The product of the HB X gene, the X protein, has multiple oncogenic effects. The hepatitis B X gene transactivates other genes, including those involved in cell turnover, and is found in an integrated form in almost all hepatitis B-related cancers. More rapid progression may occur in the presence of environmental carcinogens such as aflatoxins in the diet. However, people with chronic hepatitis B infection from endemic regions retain their high risk of HCC even if they migrate to countries with low levels of environmental carcinogens. Women are less likely to maintain persistent hepatitis

B infection than men, or to develop HCC if they remain carriers through middle age. The incidence of HCC is two to four times greater in men than in women. This may be explained, in part, by the fact that males are generally more likely to be co-infected with hepatitis C, consume alcohol and smoke cigarettes (McGlynn & London 2005).

The greatly increased risk of developing HCC associated with chronic hepatitis B infection was unequivocally demonstrated by surveys of middle-aged male civil servants in Taiwan (Beasley et al. 1981). In this study, 22,707 men were prospectively followed for HBsAg status and mortality. Forty-one subjects died from HCC and all but one were HBsAg negative. A similar increase in risk for people with chronic hepatitis B infection has been reported from many different countries, with both high and low overall adult hepatitis B prevalence rates. The risk of HCC from chronic hepatitis B infection is far higher than that observed among individuals with liver cirrhosis from other causes (Cantarini et al. 2006).

The impact

Worldwide, there were more than 600,000 deaths due to primary liver cancer in 2002 (Perz et al. 2006). Among primary liver cancers worldwide, hepatocellular carcinoma (HCC) represents the major histologic type and is likely to account for 70% to 85% of cases (Perz et al. 2006). HCC is the tenth leading cause of death from *any* condition and is the fifth most common malignancy in males and the eighth in females (Lavanchy 2004; WHO 2004). Hepatitis B and C infections account for an estimated 78% of HCC globally (53% and 25%, respectively); however, the relative percentage of HCC cases linked to hepatitis B (and/or hepatitis C) varies by geographic setting. In addition to HCC, an estimated 446,000 cirrhosis deaths related to hepatitis B and C occurred in 2002 (Perz et al. 2006). The lifetime risk of death from hepatitis B-related HCC or cirrhosis is estimated to be 25% for a person who becomes chronically infected during childhood (Bonilla & Roberts 2005; Roberts & Kemp 2007).

Data on the incidence and mortality from primary liver cancers in Australia are shown in Tables 3.1 and 3.2 below. The majority of liver cancers are HCC (as determined by ICD-10 code C22.0), but these data include other tumours such as cholangiocarcinoma, hepatoblastoma and tumours without histological confirmation. These data demonstrate the increase in primary liver cancers between 2001 and 2005, similar to that reported elsewhere (Amin et al. 2007) and to what has been seen in the past two decades, when the incidence of HCC almost doubled in both men (from 2.06 to 3.97 per 100,000) and women (from 0.57 to 0.99 per 100,000) from 1978 to 1997 (Law et al. 2000).

Precise information regarding the number of cases of HCC due to hepatitis B infection Australia-wide is not available. However, a recent longitudinal study in NSW using data linkage found that of 2072 cases of HCC identified from 1990 to 2002, 323 (15.6%), 267 (12.9%) and 18 (0.8%) were linked to hepatitis B, hepatitis C and hepatitis B/hepatitis C co-infection notifications respectively (Amin et al. 2007). A younger age at diagnosis of HCC and birth outside of Australia (particularly Asia) were associated with hepatitis B-linked cases. However, the rates of hepatitis B and C infection among people with HCC in this study may have been underestimated due to limitations of the data used in the analysis and factors such as underreporting and testing of hepatitis B and C infection, particularly in earlier years. A smaller Victorian study of 96 people with cirrhosis who had developed HCC reported that approximately 15% were HBsAg positive (and 30% hepatitis C antibody positive) (Kemp et al. 2005).

The rise in HCC is thought to be associated with a number of factors, many of which are related to hepatitis B (and hepatitis C) infection. An analysis of HCC epidemiology in an Australian tertiary hospital from 1975–2002 reported that between 1995 and 2002, people with HCC were more likely to be male, aged less than 64 years, non-Caucasian and born overseas, in comparison to patients with HCC between 1975 and 1983 (Roberts & Kemp 2007). This is consistent with an increase in the average age of immigrants from high-risk hepatitis B endemic countries, bringing more individuals into the age groups at risk. Secondly, the prevalence of chronic hepatitis C has risen in Australia and is associated with HCC cases. Co-infection with hepatitis C and hepatitis B is known to increase the risk of developing HCC (Amin et al. 2006a; Amin et al. 2006b; Amin et al. 2007). A recent Australian study describing cancer incidence in people with hepatitis B, hepatitis C or a co-infection with both viruses found that the risk of HCC was 20 to 30 times greater than in the uninfected population (Amin et al. 2006a).

Although in developed countries the mean duration from onset of chronic hepatitis B infection to the diagnosis of HCC is 35 years (Craxi & Camma 2005), in countries where hepatitis B is highly endemic, HCC can develop in children and across all age groups but is uncommon before the age of 30 (Lavanchy 2005; McGlynn & London 2005; Raza, Clifford & Franceschi 2007; Villeneuve 2005). Given that since 1991 there have already been over 90,000 chronic hepatitis B infection cases notified in Australia, the future burden of HCC will continue for many years to come, before the impact of the universal hepatitis B vaccine on HCC will become apparent.

Table 3.1 Incidence data for primary liver cancers from 2005 compared with 2001[#]

	New cases	ASR*	% change ASR (last 10 years)	% of all cancer	% increase in cases 2001–2005
Male	718	7.4	+2.9%	1.3%	62%
Female	261	2.2	+4.8%	0.6%	53%

*ASR = age standardised rate per 100,000 (Australian 2001 population standard)

[#]Includes intrahepatic bile duct cancer

Source: AIHW et al. 2005

Table 3.2 Mortality data for primary liver cancers[#]

	Deaths	ASR*	% change p.a. ASR (last 10 years)
Male	596	6.1	+1.9%
Female	346	2.9	+4.6%

*ASR = age standardised rate per 100,000 (Australian 2001 population standard)

[#]Includes intrahepatic bile duct cancer

Source: AIHW 2005

In 2001, the direct costs of managing people with chronic hepatitis B infection in Australia were estimated to range from \$1233 for a person with non-cirrhotic chronic hepatitis B infection to \$144,392 for a person requiring a liver transplant. Direct costs for HCC were \$11,753 and the average cost for palliative care for a person with chronic hepatitis B infection and HCC was \$6307 (Butler et al. 2004).

The challenge

Hepatitis B is transmitted through percutaneous or mucous membrane contact with infected blood or body fluids: in healthcare and other settings, by needle/syringe sharing, in sexual intercourse and possibly through the sharing of household items, such as razor blades. Worldwide, transmission is most common from mother to child, around the time of birth. The challenge is to protect against transmission wherever possible. Prevention measures are described below.

Effective interventions

Vaccination

The hepatitis B vaccine has been available for over 20 years and was the world's first cancer prevention vaccine (Beasley et al. 1983; van der Sande et al. 2006). In the early 1980s, a plasma-derived hepatitis B vaccine prepared from the inactivated plasma of people with chronic hepatitis B infection was used in Australia and internationally. In the late 1980s, a hepatitis B vaccine manufactured by recombinant DNA technology became available and replaced the plasma-derived vaccine in most countries, including Australia (Yu, Cheung & Keeffe 2004). The gene for the major 'surface' antigen (HBsAg) of the hepatitis B virus is expressed in yeast cells. The hepatitis B vaccines currently available in Australia are monovalent, meaning the vaccine only contains hepatitis B antigen, or combination vaccines that contain hepatitis B antigen and other antigens such as diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B, poliomyelitis and hepatitis A antigens (NHMRC 2008).

In Australia during the early 1980s, hepatitis B vaccination was initially administered to at-risk groups such as healthcare workers. In 1987, hepatitis B vaccination of infants born to mothers who were hepatitis B surface-antigen-positive commenced. In 1997, routine adolescent hepatitis B vaccination was introduced, followed by universal infant vaccination in May 2000. The adolescent program will continue until all children born since 2000 reach adolescence (NHMRC 2008; Williams 2002).

The Australian National Immunisation Program currently includes a single dose of hepatitis B vaccine at birth or up to eight days of age followed by three doses of hepatitis B vaccine at two, four and either six or 12 months of age. Adolescents aged between 12 and 15 years receive either a two-dose schedule (adult dose vaccine) administered at a 0 and four- (or six-) month interval; or a three-dose schedule (paediatric dose vaccine) at 0, one- and six-monthly intervals, predominantly through school-based programs. Adults receive a three-dose schedule of hepatitis B vaccine administered at 0, one and six-monthly intervals (AHC 2006; Yuen et al. 2004).

Hepatitis B vaccines are recommended in adults (or those not previously immunised) in the following at-risk groups (NHMRC 2008; Williams 2002):

- household contacts of people with acute and chronic hepatitis B
- sexual contacts of people with acute and chronic hepatitis B
- people on haemodialysis, people who are HIV-positive and other adults with impaired immunity
- injecting drug users
- recipients of concentrated blood products

- people with chronic liver disease and/or hepatitis C (who are seronegative for hepatitis B)
- residents and staff of facilities for people with intellectual disabilities
- people adopting children from overseas
- liver transplant recipients (who are seronegative for hepatitis B)
- inmates and staff of long-term correctional facilities
- healthcare workers, ambulance personnel, dentists, embalmers, tattooists and body-piercers
- police, members of the armed forces and emergency services staff if at risk of exposure to body fluids
- funeral workers and other workers who have regular contact with human tissue, blood or body fluids and/or used needles or syringes
- people travelling to regions of intermediate or high endemicity, either long term or for frequent short terms
- sex industry workers.

Although vaccine-induced antibody levels decline with time and may become undetectable, booster doses are not recommended in immuno-competent individuals after a primary course, as there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection (NHMRC 2008; Williams 2002). This applies to children and adults, including those at risk of occupational exposure, such as healthcare workers and dentists (Fitzsimons et al. 2005; Petersen et al. 2004).

During the late 1980s, perinatal transmission of hepatitis B was recognised as the major factor leading to virus persistence and chronic liver disease and HCC. Vaccination of newborn infants of mothers with chronic hepatitis B infection was shown to be effective in reducing viral transmission, especially if combined with administration of 'hyperimmune' hepatitis B immunoglobulin (HBIG) at birth. Hepatitis B vaccine given in combination with one dose of HBIG to babies within 12–24 hours after birth is around 85% to 95% effective in preventing hepatitis B infection (Beasley et al. 1983; Chang & Chen 2002; Kripke 2007; Lee et al. 2006; Petersen et al. 2004; WHO 2004; Yu, Cheung & Keeffe 2004). In Australia, all antenatal women are tested for hepatitis B or the hepatitis B status of mother is determined upon presentation in labour if unknown. Infants born to hepatitis B surface-antigen-positive mothers or those of unknown status should receive HBIG at birth as well as the hepatitis B vaccine.

The effect of vaccination on carriage rates in vaccinated age cohorts has been reported in many countries (Chang 2003; Chang et al. 2005; Chang & Chen 2002; Clements et al. 2006; Chen 2005; Yu, Cheung & Keeffe 2004). More time must elapse before these cohorts reach the age of greatest HCC prevalence, but already some countries with previously very high HCC rates, such as Taiwan, have observed statistically significant reductions in young, vaccinated age groups (Chang & Chen 2002; Yuen et al. 2004). Taiwan introduced a universal hepatitis B vaccination program for infants in 1984; while HCC is uncommon in children, the reported incidence of HCC fell by 75% in children aged six to nine years who were born after the program started (Chang 2003; Lee, Hsieh & Ko 2003).

The use of the hepatitis B vaccine and HBIG has been shown to be cost effective even in countries such as Australia with a low prevalence of hepatitis B. In the late 1990s, the World Health Organization advised the introduction of universal vaccination for all infants born in countries where the prevalence of chronic hepatitis B infection exceeded 2%. However, universal hepatitis B vaccination has been undertaken only sporadically in many

countries, primarily due to limited resources. Data from the World Health Organization in 2005 indicate that although 158 out of 192 (82%) of member states had introduced a routine infant immunisation program, only 119 countries could report coverage of three doses at levels greater than 80% (ACT-HBV APSCM 2006; WHO 2004). As such, hepatitis B and its complications remain a global concern (WHO 2004).

Other interventions

Transmission of hepatitis B in healthcare settings has been greatly reduced by screening of blood donations prior to transfusion or manufacture of blood products, and screening of organ donors prior to transplant (Hilleman 2003). In addition, the use of standard precautions in the clinical setting to minimise transmission of blood-borne viruses and other infection control measures—such as the use of disposable equipment, sterilisation of multi-use equipment and the correct disposal of sharps, body fluids and other body parts—has further minimised the risk of hepatitis B transmission in the healthcare setting.

Treatment of chronic hepatitis B infection, cirrhosis and HCC

The medical treatment of people with established chronic hepatitis B infection is targeted at reducing the hepatitis B replication, which in turn can potentially prevent or slow progression to cirrhosis and HCC.

In a very small percentage of people with chronic hepatitis B infection, there may be resolution of the infection. The choice of therapy varies, depending on the viral load and extent of hepatic damage; however, the ultimate aim of treatment is sustained viral suppression that results in normal ALT levels, a decrease in hepatitis B DNA and prevention of the sequelae of infection (ACT-HBV APSCM 2006; Okanoue & Minami 2006). Nucleoside analogue drugs such as lamivudine and entecavir suppress hepatitis B virus replication very effectively, although emergence of resistance is a serious problem, particularly in the case of lamivudine (ACT-HBV APSCM 2006; Fung & Lok 2004; Locarnini & Omata 2006).

PEG-interferon suppresses hepatitis B replication in a majority of individuals and achieves sustained virological control (ongoing low or undetectable levels of hepatitis B viraemia) in about a third (ACT-HBV APSCM 2006; Farrell & Teoh 2006; Ghany & Doo 2004; Hoofnagle et al. 2007). Virological control, whether spontaneous or after treatment, greatly reduces the subsequent risk of HCC; however, it has no effect on the course of established liver cancer. As most people with chronic hepatitis B infection are completely asymptomatic, a policy of monitoring and treating those with the highest risk of HCC (e.g. those with hepatitis B viral load above 2000 IU/mL and age above 40 years) may be the most effective strategy. This would require effective screening and detection programs to identify people with chronic hepatitis B infection.

Treatment of HCC itself is difficult because of the multifocal nature of the tumour and its inaccessibility. Techniques for destruction of tumour nodules depend on accurate localisation, and, although they do prolong life, they are seldom curative. Unfortunately blood tests for tumour markers have not proved reliable as screening tests, and effective chemotherapy is still lacking (Hilleman 2003; Kemp et al. 2005; O'Brien, Kirk & Zhang 2004). Imaging techniques have been employed to monitor known carriers, especially those who have developed cirrhosis and/or are entering middle age. Liver transplantation and removal of the entire liver is regarded as the most likely treatment to achieve cure, but prior spread beyond the liver may already have occurred and this has proved difficult to assess (Kemp et al. 2005).

The policy context

The bleak outcome of HCC makes prevention an especially desirable public and personal health policy. Prevention of persistent hepatitis B infection by universal infant vaccination is clearly the most significant measure, and since 2000 it has achieved global acceptance and support (Hipgrave, Maynard & Biggs 2006; WHO 2004). It will be many years before this is manifested in a falling prevalence of HCC. In the meantime, treatment of established hepatitis B infection and reduction of exposure to other factors that increase the risk of developing chronic liver disease, such as alcohol and aflatoxins, can reduce the proportion of infected people who develop chronic liver disease and HCC. The appropriate schedules for early tumour detection in people with established cirrhosis have yet to be established in Australia and there are also ongoing evaluations of different methods of surgical treatment (Roberts & Kemp 2007).

Primary prevention of hepatitis B by vaccination is now provided for all Australian infants as part of the National Immunisation Program described above. This provides optimum protection against infection in early life, when the likelihood of developing persistent infection is very high, and also provides ongoing immunity into adolescence and adult life. Uptake of hepatitis B vaccine in Australian children is very good, with three-dose coverage reported in 94.7% of infants aged 12 months and 95.9% of children aged two years (ACIR 2006).

However, despite good vaccine coverage in infants, children and school-based delivery to unimmunised adolescent groups in Australia, hepatitis B vaccination has been consistently underused by adults in high-risk groups who would not have been targeted by universal infant and childhood immunisation because of their age (Tawk et al. 2006b; Yuen et al. 2004). Low vaccine uptake rates among high-risk adults have generally been due to a lack of awareness, failure to identify and offer vaccination to at-risk persons, the cost of accessing the hepatitis B vaccine and failure to complete a course of the hepatitis B vaccine. At-risk groups, in particular people from culturally and language diverse communities, Indigenous Australians, injecting drug users, inmates of correctional facilities and men who have sex with men, need to have ready access to hepatitis B vaccines, potentially via targeted campaigns.

There is evidence that universal immunisation of infants and children in Australia is having an impact, with the number of cases of acute hepatitis B declining between 2001 and 2006 from 415 to 295 (from 2.1 to 1.6 per 100,000 population) (NHMRC 2008). It is likely that these declining rates also reflect changing practices among other risk groups, such as sex workers and intravenous drug users. However, while incident hepatitis B may have declined as a result of vaccination, the impact from the pool of people with chronic hepatitis B infection—many of whom may not be recognised as such—is still to be felt. It will be several more decades before they reach middle age, when HCC is most likely to develop. In most high prevalence countries, vaccination was introduced even more recently so that adult immigrants from these countries still have high hepatitis B carriage rates (Farrell & Teoh 2006; Tawk et al. 2006a; Tawk et al. 2006b). This means that for many years to come the pool of adult hepatitis B carriers in Australia will be relatively static or may even grow, as will the prevalence of hepatitis B-related HCC.

There are two options for reducing the disease burden from those with established chronic hepatitis B infection. The first is to treat people with chronic hepatitis B infection before they develop cirrhosis. There is good evidence that the risk of HCC is greatly reduced if viral replication is controlled either spontaneously or with treatment. Although between 0.5% and 1% of the adult population have chronic hepatitis B infection with detectable virus in their blood, a minority are aware of their infected status or assessed for treatment (Gidding et al. 2007; O'Sullivan et al. 2004; Wood et al. 2005). Apart from antenatal

screening, case finding has not been promoted as a public health priority, and there is generally no systematic arrangement for referral and assessment of individuals who are found to be HBsAg positive in the course of ordinary medical care, although many of these are notified under the current laboratory-based reporting system. Cost-benefit analyses of hepatitis B treatment strategies do not yet include the expense of case finding, and there is debate in the literature about the benefit of treatment of non-cirrhotic patients, whose infection may clear spontaneously over time.

The second option for reducing the disease burden of HCC is to institute screening for cancer nodules in the livers of people with established cirrhosis. If small and single, the nodules can be treated by resection of the affected lobe of the liver. If large or multiple, injection of the lesions with cytotoxic drugs may prolong life (Craxi & Camma 2005; Hilleman 2003; Kemp et al. 2005). In summary, the current approaches to secondary prevention of HCC in those with established hepatitis B infection have not yet attained a sufficiently firm scientific basis to justify their introduction on a nationwide scale.

In 2006, the Australian Hepatitis Council issued a position paper outlining a number of actions that members believe are necessary to address hepatitis B in Australia. These include (ACT-HBV ANZLC 2007; AHC 2006):

- the development and implementation of a national hepatitis B strategy
- the development of health maintenance and support resources for people with chronic hepatitis B infection
- broad research that encompasses both the social and health impacts of hepatitis B infection
- representation of people living with chronic hepatitis B infection on any national strategic council and an ongoing campaign to raise awareness of hepatitis B
- vaccinations and treatment among high-risk groups.

Despite the gains that will be made through universal vaccination of infants, many further measures require consideration in an overall strategy to reduce the future burden of disease from HCC

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