Chronic viral hepatitis and hepatitis B virus infection: stop the cancer

The World Health Organization (WHO) estimates that 2 billion people have been infected with hepatitis B virus (HBV). Despite an efficacious vaccine having been available since 1982, there are currently 350 million people, predominantly in Asia, suffering from chronic HBV infection. Of these chronically infected individuals, approximately 25% will develop liver cancer, which is the fifth most common cancer worldwide, ranking third as a cause of cancer mortality. In Australia, by 2007 liver cancer had become the 11th most common cause of cancer mortality as well as the fastest increasing cause of cancer mortality, reflecting the increasing prevalence of viral hepatitis.

Hepatitis is the term describing inflammation of the liver and viral hepatitis means the liver inflammation is caused by a virus. The five most common causative agents of viral hepatitis are designated hepatitis A virus, HBV, hepatitis C virus (HCV), hepatitis D virus and hepatitis E virus. While infection with any of these viruses can lead to the classic hepatitis symptoms of dark urine, yellowing of the eyes and skin (jaundice) and anorexia, the viruses are otherwise unrelated, using different replication strategies that divide them into separate taxonomic families.

Unlike many viral infections where recovery is associated with immunity and life-long protection, a proportion of those infected with HBV or HCV develop chronic infection in which the virus continues to replicate in the liver. This chronic carriage of HBV or HCV can lead to progressive liver disease, which after many years can result in cirrhosis and liver cancer. Around 25% of people infected with HCV will clear the virus spontaneously but the remainder develops chronic infection. For HBV, the age at which the infection is acquired is the major factor that determines clearance or chronicity. Chronic infection is the predominant outcome if infected early in life (>90%), whereas healthy adults are unlikely to become chronically infected (<5%). In many developing countries, HBV is transmitted from chronically infected mothers to their babies, who in turn become chronically infected, perpetuating the cycle of transmission. It had been proposed that the ability of the virus to persist in the newborn and infants is due to an immune tolerance caused by the secreted hepatitis B ‘e’ antigen (HBeAg), which can cross the placenta. Recent work has confirmed that HBeAg can modulate the innate immune pathway by suppression of Toll-like receptors.

Diagnosis of HBV infection relies on interpretation of serological assays designed to detect viral antigens and their corresponding antibodies. The most useful marker is serum hepatitis B surface antigen (HBsAg), a non-infectious mosaic of the viral surface glycoproteins that circulate in the blood in great excess during the course of infection. This was the so-called Australia antigen, originally discovered by Blumberg and colleagues in the blood of an Aboriginal Australian when investigating immunological variation of complement proteins. It was some time before the association of this protein with hepatitis B was established but its public health significance was subsequently recognised. Blumberg was awarded a Nobel Prize in 1976 and further acknowledged recently when 28 July was declared World Hepatitis Day, the date of Blumberg’s birthday. Detection of HBsAg is now carried out by automated immunoassays and the persistence of HBsAg for longer than 6 months defines chronic HBV infection.

The advent of molecular testing for HBV DNA has also shown the importance of this marker of viral replication. Quantification of HBV DNA is required to determine patient eligibility for treatment and for monitoring the efficacy of treatment. In large population studies carried out in Taiwan, the HBV DNA load has been shown to be independently associated with the incidence of cirrhosis and liver cancer with a positive correlation between viral load and the development of liver disease. The corollary of this is that antiviral therapy that successfully reduces HBV DNA load will reduce the incidence of liver injury. Indeed, antiviral therapy with nucleotide or nucleoside analogues that inhibit virus replication has been shown to significantly reduce the frequency of liver cancer.

Recent decreases in the incidence of liver cancer in regions endemic for HBV have been reported that may be related to an increased uptake of vaccine and greater awareness of viral transmission routes.
However, cases of liver cancer are increasing in low incidence regions such as North America, France and Australia\(^6\). The burden of chronic HBV infection in Australia has been very recently evaluated and for 2011 the number of people living with chronic HBV infection was estimated to be 218,000, for a population prevalence of 1%\(^7\). The majority of those with chronic infection were born overseas in endemic area of the Asia Pacific; Aboriginal and Torres Strait Islander people were another group disproportionately represented\(^7\).

Expert advocacy has propelled viral hepatitis into public awareness internationally. The Global Burden of Disease Study 2010 estimated that the total number of deaths attributable to HBV infection was 786,000, and when combined with 499,000 deaths from HCV infection, viral hepatitis ranks as one of the most frequent causes of human mortality\(^8\). The World Health Assembly adopted a resolution in 2010 calling for a wide-ranging approach to the prevention and control of viral hepatitis\(^9\), resulting in the establishment of the inaugural WHO Global Hepatitis Program. In Australia, the first National Hepatitis B strategy (2010–2013) has been developed, as has a National HBV Testing policy. The Cancer Council of Australia has provided a chapter devoted to liver cancer in its National Cancer Prevention Policy and healthcare workers can access online information and advice in the investigation and management of people with HBV infection (HepBHelp.org.au). Further promotion and implementation of the strategies outlined in many of these documents will be of great benefit to public health and help us redress the damage caused by this insidious virus.

### References


### Biography

**Scott Bowden** is the Head of the Molecular Microbiology Laboratory at the Victorian Infectious Diseases Reference Laboratory and also is an adjunct Associate Professor in the Department of Microbiology at Monash University. He has served on Government committees developing the National Testing Strategies for Hepatitis B and Hepatitis C as well as the National HBV Testing policy.