How the discovery of Australia antigen led to the creation of hepatitis B vaccine

Although eradication of hepatitis B remains a distant goal, the development of the hepatitis B vaccine has, nonetheless, reduced infection rate and deaths. Jenny Bryan takes a look at the development of the vaccine in this month’s article on landmark drugs

Nearly 30 years after it was originally licensed, hepatitis B vaccine has been incorporated into the national infant immunisation programmes of at least 177 countries worldwide. But, with an estimated two billion people worldwide infected with the hepatitis B virus (HBV) and about 350,000 living with chronic infection, eradication remains a distant goal. Around 600,000 deaths are thought to be caused by hepatitis B each year and 25 per cent of adults who were chronically infected during childhood are likely to die later from liver cancer or cirrhosis. But leading authorities, such as Arie Zuckerman, emeritus professor of medical microbiology at University College Medical School, London, are convinced that the figures would be much higher without hepatitis B vaccine.

“Immunisation has resulted in a dramatic reduction in the prevalence of infection, as well as a very marked reduction in the carrier rate and progression to chronic hepatitis B and primary liver cancer in many countries, such as China, Japan, Taiwan and Singapore,” points out Professor Zuckerman, formerly the Royal Free Hospital School of Medicine and director of the World Health Organization Reference Centre on Viral Diseases.

Discovery of Australia antigen
Outbreaks of jaundice likely to have been caused by HBV date back to before the 19th century. But the viral cause remained elusive until 1964, when Australia antigen — so called because it was first identified in the serum of an Aboriginal Australian — was isolated from the serum of leukaemia patients, and later from patients with transfusion-associated hepatitis. Further research linked Australia antigen to virus-like particles, and the antigen — now known to be on the surface of HBV and renamed hepatitis B surface antigen (HBsAg) — soon became the focus of efforts to develop a vaccine against the infection.

Early vaccines were highly purified and inactivated forms of HBsAg extracted from the plasma of healthy HBV carriers. The first large-scale clinical trial in over 1,000 homosexual men at high risk of HBV infection showed a reduction in infection of up to 92 per cent during an 18-month period following immunisation. A plasma-derived vaccine, developed by Merck and Co, was licensed in the UK in 1982. But, despite reassuring safety tests, the emerging AIDS epidemic raised concerns about the use of plasma-derived vaccines, and sent Merck and other pharmaceutical researchers back to their laboratories to develop alternatives.

Recombinant DNA technology was in its infancy, but Merck worked with researchers at the Universities of California and Washington, who had cloned the HBsAg gene and inserted the DNA into the yeast Saccharomyces cerevisiae to produce the recombinant hepatitis B vaccine, which was then licensed in 1986.

Current and future vaccines
In the UK, recombinant hepatitis B vaccine is available in both monovalent formulation and as a bivalent vaccine with hepatitis A. In other countries, it is also combined with diphtheria, tetanus-pertussis, haemophilus influenzae b and inactivated polio.

The three-dose hepatitis B vaccine schedule induces protective antibody concentrations in over 95 per cent of healthy infants, children and young adults. Response rates are lower in those immunised over the age of 40 years.

Between 5 and 10 per cent of healthy immunocompetent individuals do not respond to current HBsAg vaccines, but revaccination in non-responders may be effective. Among the likely reasons for a failure to respond are genetic variations in human leukocyte antigen-mediated immune responses. Third-generation DNA vaccines, which include additional domains of the HBsAg protein — notably pre-S1 and pre-S2 — have been shown to induce protective antibody levels in people who fail to respond adequately to standard vaccines. These have been marketed in some countries, but cost has impeded their wider uptake.

Hepatitis B transmission
Immunisation programmes following the introduction of hepatitis B vaccine have been shaped by the discovery of the importance of mother-to-child transmission of the virus. In an early study in Taiwan, nearly a third of babies born to carrier mothers were found to be HBsAg positive, and most had become antigenaemic within the first six months of life. Subsequent studies showed even higher transmission rates in some populations, especially in women with the hepatitis B e-antigen, which is indicative of active viral replication in the liver.

“Mother-to-child transmission is the most important factor in establishing the chronic carrier state of HBV in 70–90 per cent of
“Immunisation programmes following the introduction of hepatitis B vaccine have been shaped by the discovery of the importance of mother-to-child transmission of the virus”

infants born to e-antigen-positive mothers, especially in areas with highest transmission rates, such as South East Asia and the Pacific Basin, followed by African Caribbean and Indian populations, with lowest levels among Caucasians,” explains Professor Zuckerman.

As early as 1991, a WHO advisory committee recommended that hepatitis B should be added to national immunisation programmes and it later set a target of an 80 per cent reduction in new child carriers of HBV by 2001.4 Thanks to the widespread response to the recommendation, WHO estimated that over two-thirds of babies born in 2008 in countries with EBV immunisation programmes received three doses of vaccine.5

The UK remains one of the small number of countries, mainly in Europe, that do not include hepatitis B in their childhood immunisation programmes. Instead, immunisation is recommended for those at high risk of contracting the infection. These include babies whose mothers have had acute hepatitis B during pregnancy or are positive for hepatitis B surface-antigen (regardless of e-antigen markers). In 2009, the Joint Committee on Vaccination and Immunisation concluded that universal HBV vaccination would not be cost-effective. But, earlier this year, the Board of Science of the British Medical Association reaffirmed its support for universal immunisation in childhood, concluding that data suggested that universal vaccination of infants would be more cost-effective than the current selective targeting of vaccination at high-risk groups.

Professor Zuckerman points out that 30–50 per cent of cases of hepatitis B occur in people without any known risk factors for the disease and that immunising only those deemed to be at high risk has not controlled hepatitis B in any country with low endemicity in which it has been used.

“This alone is a reason to implement universal immunisation but, if this is not introduced, we should at least screen and immunise immigrants and asylum seekers from countries where hepatitis B is highly endemic,” he says. “Since mother-to-child transmission is so important, it follows that school children who were born in countries of high endemicity may form an important reservoir of hepatitis B and should be immunised routinely,” he adds.

Recently published data from a study carried out in The Netherlands on the impact of immunising infants with at least one parent born in a country with high HBV endemicity showed a significant reduction in incidence from 2.9/106 per years before the programme was started to 0.3/106 years after implementation.6 Similarly, a recent analysis of the impact of widespread HBV immunisation in the US showed that the prevalence of antibody to hepatitis B core antigen (anti-HBc) in children aged 6–19 years fell from 1.9 per cent during the period 1986–94 to 0.6 per cent (P<0.01) between 1999 and 2006.7

Professor Zuckerman concludes that the long-term cost benefits of eradicating hepatitis B, even in countries where the condition is less common, such as the UK, outweigh the immediate costs of universal immunisation: “The lifetime morbidity and mortality from hepatitis B — in terms of chronic liver disease and liver cancer — are greater than for any other vaccine preventable disease. We have a highly effective and safe vaccine, and we have a childhood immunisation programme already in place to which hepatitis B could be added. Investing in universal childhood HBV vaccination now would have far-reaching benefits for the UK population in the future.”

References