

# PRIMARY PREVENTION OF HEPATITIS B VIRUS INFECTION

# 5

**Nghi Phung**

Department of Drug and Alcohol, Department of Gastroenterology and Hepatology, Westmead Hospital, Westmead, NSW.

**Nicholas Wood**

National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Children's Hospital at Westmead, Westmead, NSW.

## KEY POINTS

- Universal hepatitis B vaccination programs have had a profound impact on reducing the incidence of chronic hepatitis B infection.
- All infants should receive hepatitis B vaccination, with the first dose given at birth.
- Adolescents not vaccinated in childhood are recommended to receive hepatitis B vaccines.
- HBIG should be given to infants born to HBsAg-positive mothers within 12 hours of birth and the first dose of HBV vaccine should be administered concomitantly.

## Introduction

Hepatitis B vaccination aims to prevent hepatitis B virus (HBV) infection and its complications, which include fulminant hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC). In acute cases, fulminant hepatitis occurs rarely, but is associated with significant mortality, especially in infants.<sup>1</sup> The bulk of the disease burden is in chronic infection. Chronic hepatitis B (CHB) develops in about 90% of infants who acquire the infection at birth, 20–50% of children who acquire the infection between 1 and 5 years of age and about 1–10% of older children and adults who acquire HBV infection.<sup>2</sup>

The World Health Organization (WHO) strategy for the control of HBV infection aims to provide universal infant hepatitis B immunisation, with the first dose given at birth.<sup>3</sup> The vaccine induces antibodies to hepatitis B surface antigen (anti-HBs) and a titre of 10 IU/mL or more is considered to be protective against the HBV infection. With the introduction of universal infant vaccination programs in countries with a high prevalence of hepatitis B such as Taiwan the immunisation against hepatitis B has had a profound impact on reducing the incidence of chronic infection, dropping the HBsAg

prevalence rate in children from 10% to 1%<sup>4</sup> and halving the incidence of HCC in children aged 6 to 14 years.<sup>5,6</sup>

In Australia, the impact of universal vaccination on the incidence of hepatocellular carcinoma will not be evident for at least another 15 years.

## Target groups for vaccination in Australia

Transmission of HBV is a result of inoculation or mucosal contact with blood or body fluids from people with HBsAg-positive HBV infection. Transmission of HBV through blood transfusion and organ transplant has been almost entirely eliminated due to the screening of blood and organ donors in Australia. However, there remains a small risk of exposure to HBV for patients with clotting disorders who receive blood-product concentrates.

The modes of transmission still relevant in Australia include:

- Perinatal
- Household contacts
- Sexual contact
- Reuse of injecting or tattooing equipment
- Occupational exposure

In addition to screening blood, organ donors and health care workers for HBV, the strategy to control HBV infection in Australia, which began in 1988, includes vaccination and hepatitis B immunoglobulin (HBIG) given at birth to neonates born to HBsAg-positive mothers. In the Northern Territory, the hepatitis B vaccine has been routinely given at birth to Aboriginal and Torres Strait Islander infants since 1988 and to all infants since August 1990. HBV vaccination for all adolescents commenced in 1997 in some States and Territories, and the universal infant HBV vaccination program began in 2000 with the first dose given at birth. The adolescent program will continue until those immunised for hepatitis B in the childhood program reach adolescence.

Groups at risk of exposure or significant morbidity from exposure to HBV infection should be targeted for vaccination, including:

(1) As part of the Australian National Immunisation Program:

- Infants
- Adolescents aged between 10 and 13 years

(2) People exposed to community groups with high prevalence of HBV infection (Table 5.1):

- Men who have sex with men (MSM)
- Female commercial sex workers (FCSW)
- Aboriginal and Torres Strait Islander people
- Injecting drug users (IDU)
- Prison inmates
- Cultural and linguistically diverse (CALD) communities
- People adopting children from overseas countries with high prevalence rates
- Frequent or long-term travellers to endemic areas
- Household contacts of people with acute and chronic hepatitis B

The risks in CALD groups reflect the rates of chronic infection in first generation immigrants from countries with high prevalence of HBV infection. The high prevalence of HBV infection in the Aboriginal and Torres Strait Islander population reflects the barriers for access to public health education and vaccination. The risks in MSM, FCSW, IDU and prison inmates often relate to unsafe practices, for example,

inmates who engage in amateur tattooing, homosexual contact and reusing injecting equipment. While the burden of disease is largely carried by people born in endemic regions, a significant portion (40%) of acute cases result from the unsafe use of injecting drugs, which reflects the low uptake of vaccination in this group.

**Table 5.1: Prevalence of chronic hepatitis B in Australia by risk group**

Group	HBsAg prevalence in risk group (%)	Proportion of CHB in Australia (%)
Blood donors	0.1	N/A
MSM	3.3	8
Indigenous communities	2.3 (urban) 8.2 (rural) 12 (prisoners)	16
CALD communities	0.9 (Middle East/ Africa) 3.7 (Pacific Islands) 4.9 (NE Asia) 5.4 (SE Asia)	16 (NE Asia) 33 (SE Asia)
IDU	1.6	5
Prison inmates	1.6-3.0	
<small>Modified from O'Sullivan et al. 2004<sup>5</sup>            CHB: chronic hepatitis B            MSM: men who have sex with men            CALD: cultural and linguistically diverse            IDU: injecting drug user</small>		

(3) People prone to exposure or at risk of significant morbidity from exposure:

- Haemodialysis patients
- Patients with clotting disorders
- Human immunodeficiency virus (HIV) positive and other immunosuppressed people
- Transplant recipients
- Patients with chronic liver disease or hepatitis C
- Intellectually disabled people

(4) People at risk of occupational exposure:

- Health care workers, dentists, police, tattooists, body piercers
- Staff of facilities for people with intellectual disabilities
- People playing contact sport.

## Vaccines available

### 1. Monovalent vaccines

	Hepatitis B surface antigen (HBsAg)
Engerix-B (adult formulation)	20 µg per 1 mL
Engerix-B (paediatric formulation)	10 µg per 0.5 mL
H-B-VAX II (adult formulation)	10 µg per 1 mL
H-B-VAX II (paediatric formulation)	5 µg per 0.5 mL
H-B-VAX II (dialysis formulation)	40 µg per 1 mL

### 2. Combination vaccines

- a) Combination vaccines that include both diphtheria, tetanus, acellular pertussis (DTPa) and hepatitis B
- **Infanrix HepB:** diphtheria-tetanus-acellular pertussis-hepatitis B (GlaxoSmithKline)
  - **Infanrix Hexa:** diphtheria-tetanus-acellular pertussis-hepatitisB-inactivatedpoliomyelitis vaccine-Haemophilus influenzae type b (GlaxoSmithKline)
  - **Infanrix Penta:** diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine (GlaxoSmithKline).
- b) Other combination vaccines that include hepatitis B:
- **Comvax:** Haemophilus influenzae type b – hepatitis B (CSL Biotherapies; Merck & Co Inc.)
  - **Twinrix Junior (360/10):** combined hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine (GlaxoSmithKline)
  - **Twinrix (720/20):** hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine (GlaxoSmithKline).

## Current National Immunisation Program: 2007

### Infants

All infants are recommended to receive hepatitis B vaccine within eight days of birth, followed by three further doses in infancy (Table 5.2). The type of HBV vaccine used differs between States and Territories.

Table 5.2: The National Immunisation Program for Hepatitis B<sup>11</sup>

Age	Antigen	NSW, ACT, WA, TAS	VIC, QLD, SA	NT
Birth	Hep B	monovalent	monovalent	monovalent
2 mth	Hep B	DTPa-Hib-IPV- Hep B	Hib-Hep B	DTPa- IPV- Hep B
4 mth	Hep B	DTPa-Hib-IPV- Hep B	Hib-Hep B	DTPa- IPV- Hep B
6 mth	Hep B	DTPa-Hib-IPV- Hep B		DTPa- IPV- Hep B
12mth	Hep B		Hib- Hep B	

DTPa: diphtheria-tetanus-acellular pertussis  
 Hib: Haemophilus influenzae type b  
 IPV: oral inactivated poliomyelitis vaccine

### Premature infants

Preterm babies do not respond as well to the hepatitis B vaccine as term babies.<sup>7</sup> For babies under 32 weeks gestation or less than 2000g birth weight, it is recommended to give the vaccine at 0, 2, 4 and 6 months of age and either:

- (a) measure anti-HBs at 7 months of age and give a booster at 12 months of age if antibody titre is less than 10 mIU/mL, or
- (b) give a booster at 12 months of age without measuring the antibody titre.<sup>11</sup>

### Adolescents

Adolescents not vaccinated in childhood are recommended to receive the hepatitis B vaccine. Two regimens are available:

- Three-dose regimen for adolescents aged up to 20 years: Hepatitis B (paediatric formulation): 3 doses of 0.5 mL. The optimal interval is one month between first and second dose and a third dose given five months after the second dose.
- Two-dose regimen for adolescents aged 11 to 15 years: H-B-Vax II 10 µg (adult formulation) or Engerix-B 20 µg (adult formulation) at 0 and 4–6 months.

### Accelerated vaccination schedules

Two products, Engerix-B (Adult) and Twinrix (720/20), are registered for use in accelerated schedules. Accelerated schedules should only be used if there is very limited time before departure to endemic regions (Table 5.3).

**Table 5.3: Accelerated hepatitis B vaccination schedules**

Vaccine	Age	Dose (HBsAg protein)	Volume	Schedule
Engerix-B (paediatric)	up to 20 years	10 µg	0.5 mL	0, 1, 2, 12 months
Engerix-B (adult) *	>20 years	20 µg	1.0 mL	0, 7, 21 days; booster at 12 months
Twinrix (720/20) *	>15 years	20 µg	1.0 mL	0, 7, 21 days; booster at 12 months

\* If time permits, it is recommended that the 0, 1, 2 month schedule be used, as higher seroprotective rates are observed following this schedule compared to 0, 7, 21 day schedule; a booster dose at 12 months is recommended for long-term protection.

## Catch-up vaccination schedules

If the infant received the birth dose of hepatitis B vaccine, three catch-up doses can be given 4–8 weeks apart. If the infant did not receive the birth dose, a catch-up of this dose is not necessary. In this circumstance, the hepatitis B vaccination should commence at 2 months of age. There should be a minimum interval of 8 weeks between doses 2 and 3.

## Booster doses

Although vaccine-induced antibody levels decline with time and may become undetectable, booster doses are not recommended in immunocompetent people after a primary course, as there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection.

Testing for post vaccination response four weeks after the third dose is recommended for:

- Health care workers involved with exposure prone procedures (see Chapter 11: Infection control and occupational health)
- Those at risk of severe or complicated disease (e.g. immunosuppressed patients and patients with chronic liver disease)

- Those expected to have a poor response to hepatitis B vaccine (e.g. haemodialysis patients).

## Adverse events following hepatitis B vaccination

- Soreness at the injection site (5%, common), fever (usually low grade, 2–3%, common), nausea, dizziness, malaise, myalgias and arthralgias. Fever can be expected in neonates (0.6–3.7%, common).
- Anaphylaxis has been reported very rarely in adults.
- Although various adverse events, such as demyelinating diseases, multiple sclerosis, Guillain-Barré syndrome and arthritis have been reported, there is no evidence of a causal relationship with the hepatitis B vaccination.<sup>8,9</sup>

## Hepatitis B immunoglobulin (HBIG)

Hepatitis B immunoglobulin (HBIG) is prepared from pooled plasma from the blood bank, with samples selected on the basis of high levels of anti-HBs. Use is recommended in infants born to HBsAg-positive mothers and non-immune people exposed to blood of people with CHB infection.

HBIG should be given to newborns within 12 hours of birth exposure or to adults not previously vaccinated within 72 hours of exposure, as efficacy diminishes after 48 hours. This should be followed by the administration of the hepatitis B vaccine as per the usual schedule. Previous vaccination in the exposed adult should be verified by evidence of detectable anti-HBs. If the anti-HBs is undetectable, HBIG should be administered as follows:

- 100 IU children (<30kg weight)
- 400 IU (>30kg weight)

## Non-response or vaccination failure

Firstly, HBsAg carriage should be excluded as a cause of failure in vaccine non-responders. For those subjects who have not achieved adequate anti-HBs levels ( $\geq 10\text{mIU/mL}$ ) after the third dose of vaccine, booster doses should

be given, as a fourth double dose or further three doses at monthly intervals, followed by testing for response four weeks later. Persistent non-responders should be informed about the need for HBIG within 72 hours of parenteral exposure to HBV.

Vaccination failure may occur in people exposed to HBV variants with mutations in the HBV surface gene (vaccine-induced escape mutant). Current HBV vaccines are not effective in preventing infection with these mutants. The majority of such vaccine-induced escape mutants were initially reported in neonates through vertical transmission and in transplant recipients. These vaccine-induced escape mutants were responsible for most of the 3.4% vaccine failure rate reported in the Chinese adult population undergoing an HBV vaccination program.<sup>10</sup>

### HBV vaccination programs in the CALD and Indigenous populations

CALD and Indigenous populations are confronted with different issues from the general population, which often hamper the success of vaccination programs in Australia. Language and cultural differences are obvious barriers. People not captured by the universal infant and adolescent vaccination program can present, related to their age at migration to Australia. Some practices transferred to Australia, such as eyebrow tattooing and vacuuming (a form of therapy involving the use of suction cups applied to the skin), could continue to be routes of transmission.

The high prevalence rate of HBV infection in the Indigenous population requires targeted public health policies to overcome the barriers to accessing public health education and medical services.

For further information about these recommendations, please refer to *The Australian Immunisation Handbook*. 9th Edition (2007).<sup>11</sup>

## References

1. Kao JH, Hsu HM, Shau WY, Chang MH, Chen DS. Universal hepatitis B vaccination and the decreased mortality from fulminant hepatitis in infants in Taiwan. *J Pediatr* 2001;139:349-52.
2. Heymann DL, editor. Control of communicable diseases manual. 18th ed. Washington: American Public Health Association, 2004.
3. Goldstein S, Fiore A. Towards the global elimination of hepatitis B virus transmission. *J Pediatr* 2001;139:343-5.
4. Ni YH, Huang LM, Chang MH, Yen CJ, Lu CY, You SL, et al. Two decades of universal hepatitis B vaccination in Taiwan: impact and implication for future strategies. *Gastroenterology* 2007;132(4):1287-93.
5. O'Sullivan BG, Gidding HF, Law M, Kaldor JM, Gilbert GL, Dore GJ. Estimates of chronic hepatitis B virus infection in Australia, 2000. *Aust N Z J Public Health* 2004;28(3):212-6.
6. Williams A. Reduction in the hepatitis B related burden of disease-measuring the success of universal immunisation programs. *Commun Dis Intell* 2002;26:458-60.
7. Saari TN for the American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. *Pediatrics* 2003;112:193-8.
8. Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B (review). *Expert Opin Drug Saf* 2003;2(3):225-31.
9. World Health Organization (WHO). The Global Advisory Committee on Vaccine Safety rejects association between hepatitis B vaccination and multiple sclerosis (MS). 2006. Available at: [http://www.who.int/vaccine\\_safety/topics/hepatitisb/ms/en/](http://www.who.int/vaccine_safety/topics/hepatitisb/ms/en/) (Last accessed October 2006).
10. Chuan He, Fumio Nomura, Sakae Itoga, Kazumasa Isobe, Toshiaki Nakai. Prevalence of vaccine-induced escape mutants of hepatitis B virus in the adult population in China: A prospective study in 176 restaurant employees. *J Gastroenterol Hepatol* 2001;16(12); 1373-7.
11. National Health and Medical Research Council (NHMRC). *The Australian Immunisation Handbook*. 9th Edition. Canberra: Commonwealth Department of Health and Ageing, 2007.