4.5 HEPATITIS B

4.5.1 Virology

Hepatitis B virus (HBV) contains circular, partially double-stranded DNA. The outer surface of the virus is glycolipid, which contains the hepatitis B surface antigen (HBsAg). Other important antigenic components are the hepatitis B core antigen (HBcAg) and hepatitis B e antigen (HBeAg). HBcAg is not detectable in serum, but can be detected in liver tissue in persons with acute or chronic hepatitis B infection. HBeAg, and antibodies against HBeAg (anti-HBe) or the HBcAg (anti-HBc), are serological markers of HBV infection. Antibodies against HBsAg (anti-HBs) indicate immunity, which may result from either natural infection or immunisation (in which case there would not be any markers of HBV infection). Persistence of HBsAg denotes infectivity, which is greater if HBeAg and/or HBV DNA are also positive.[1] Occult hepatitis B infection is characterised by the presence of HBV DNA in the liver (with or without detectable HBV DNA in the serum) and negative HBsAg.[2]

4.5.2 Clinical features

In approximately 30 to 50% of adults, infection causes symptomatic acute hepatitis, but in neonates and young children, particularly those <1 year of age, initial infection is usually asymptomatic.[3,4] The incubation period is usually 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 clinically indistinguishable from other forms of hepatitis, and symptoms include fever, jaundice, malaise, anorexia, nausea and vomiting, abdominal pain (especially in the right upper quadrant), myalgia, and the passage of dark-coloured urine and light-coloured stools. Jaundice may be preceded by an acute febrile illness with arthralgia or arthritis and rash, most typical of hepatitis B. During recovery, malaise and fatigue may persist for many weeks. Fulminant hepatitis occurs in up to 1% of acute cases.[1,5]

Following acute infection, approximately 1 to 10% of persons infected in adulthood,[4,6] but up to 90% of those infected in early infancy,[6] become chronically infected with hepatitis B. Persons chronically infected with HBV are identified by the long-term presence (longer than 6 months) of circulating HBsAg.[1,5] Those with occult infection may reactivate HBV infection if they become immunocompromised.

Persons with chronic HBV infection are capable of transmitting the disease, including mother-to-child peripartum transmission, though they often remain asymptomatic and may not be aware that they are infected. Most of the serious complications associated with hepatitis B occur in the context of chronic HBV infection, which is associated in up to 25% of cases with premature mortality due to cirrhosis and/or hepatocellular carcinoma.[1]

4.5.3 Epidemiology

The prevalence of chronic HBV infection differs in different parts of the world, and may be quite variable within countries. The prevalence of chronic HBV infection varies from less than 0.5% among Caucasians in the United States, northern Europe and Australia, 1 to 5% in the Mediterranean countries, parts of eastern Europe, Africa, Central and South America, up to greater than 10% in many sub-Saharan African, East and Southeast Asian and Pacific island populations.[7-10] In regions of moderate to high prevalence of HBsAg (where ≥2% of the population is HBsAg-positive), infections are mainly acquired perinatally or in early childhood.[1]

Chronic infection and its sequelae, including cirrhosis and hepatocellular carcinoma, contribute to the majority of HBV disease burden in Australia. In recent decades, the burden from such disease has been increasing, concurrent with the increasing number of immigrants from regions of high HBV prevalence.[11] Aboriginal and Torres Strait Islander people, and migrants born in Asia and Pacific islands, North Africa, Middle Eastern and Mediterranean countries, have a significantly increased prevalence of chronic HBV infection compared with the rest of the Australian-born population.[12,13] First-generation immigrants of culturally and linguistically diverse background, who are mostly from countries of high HBV endemicity, usually retain the prevalence of chronic HBV infection of their country of origin. Other population groups with an increased prevalence of markers of HBV infection include patients with HIV infection, persons who used injected drugs between 1980 and 1990, and household contacts of someone diagnosed with hepatitis between 1980 and 1990.[13] Notification of chronic HBV infection depends on levels of hepatitis B testing and reporting, and a substantial proportion of persons with chronic HBV infection remain undiagnosed. It has been estimated by mathematical modelling that, in 2010, about 170 000 people were living with HBV infection in Australia, with about 335 deaths due to HBV infection in that year.[14]

Newly acquired cases of HBV infection in Australia mostly occur in young adults, through injecting drug use, skin penetration procedures or sexual contact.[15] Between 2006 and 2010, the notification rate of newly acquired hepatitis B in Australia ranged from 1.0 to 1.4 per 100 000 population. Since 2001, the rate of diagnosis of newly acquired infections has declined substantially among people aged 15–29 years and has remained relatively stable among people aged ≥30 years.[14-16] However, some new HBV infections are asymptomatic and may go undetected.

Similar to chronic infection, higher rates of notified cases of newly acquired hepatitis B, or hospitalisation due to acute hepatitis B, have been reported among Aboriginal and Torres Strait Islander people compared with the general Australian population.[17,18] In one United States study, adults with diabetes mellitus had a greater chance of developing

acute hepatitis B disease than the general population;[19] however, there are no published Australian studies examining this.

Transmission of HBV may result from inoculation through broken or penetrated skin, or by mucosal contact with blood or other body fluids (mainly vaginal fluids and semen) from an infectious person. There are four major routes of HBV transmission:

- perinatal transmission from infected mother to neonate (vertical transmission), usually occurring at or around the time of birth
- parenteral or mucosal exposure to infected blood and other bodily fluids; common scenarios include:
  - » sharing of contaminated equipment that penetrates the skin, such as needles (among persons who inject drugs), tattoo equipment, body-piercing equipment, acupuncture equipment and razor blades
  - » needle-stick injury, for example, in a healthcare setting
  - » contact between infective body fluids and mucous membranes
- sexual contact (including vaginal or anal intercourse, although the latter is associated with a higher risk)
- non-sexual contact with an infected person (horizontal transmission), including household transmission, for example, child-to-child transmission through contact between open sores or wounds.

In Australia, screening of blood and organ donors using serological, and subsequently nucleic acid amplification, testing has virtually eliminated the risk of transmission of hepatitis B through blood transfusion and organ transplants.[20,21] Saliva may contain levels of virus that are likely to be infective only if inoculated directly into tissue (ocular or mucous membranes). The risk of transmission by inadvertent inoculation by other means, such as by toothbrush, razor etc., or through close personal contact in households in which one or more infected persons reside, is low but not negligible.[22-29]

The strategy for prevention of hepatitis B through immunisation in Australia commenced in the early 1980s, with vaccination programs targeting individuals with increased risk of HBV exposure, including infants at particular risk of infection at birth. Universal infant vaccination commenced in the Northern Territory in 1990. A universal hepatitis B vaccination program was recommended for infants and adolescents in 1996. The adolescent program commenced in some states and territories in 1997 and the universal infant program, which includes a dose given at birth, began nationally in 2000. The adolescent program will continue until those immunised for hepatitis B in the infant program reach adolescence.

4.5.4 Vaccines

Monovalent hepatitis B vaccines

- ***Engerix-B*** – GlaxoSmithKline Australia Pty Ltd (recombinant DNA hepatitis B vaccine). ***Adult formulation*** – Each 1.0 mL monodose vial or pre-filled syringe contains 20 µg recombinant hepatitis B surface antigen (HBsAg) protein, adsorbed onto 0.5 mg aluminium as aluminium hydroxide. ***Paediatric formulation*** – Each 0.5 mL monodose vial or pre-filled syringe contains 10 µg HBsAg protein, adsorbed onto 0.25 mg aluminium as aluminium hydroxide.
  Both formulations may contain yeast proteins.
- ***H-B-Vax II*** – bioCSL Pty Ltd/Merck Sharp & Dohme (Australia) Pty Ltd (recombinant DNA hepatitis B vaccine). ***Adult formulation*** – Each 1.0 mL monodose vial or pre-filled syringe contains 10 µg recombinant HBsAg protein, adsorbed onto 0.5 mg aluminium hydroxide. ***Paediatric formulation*** – Each 0.5 mL monodose vial or pre-filled syringe contains 5 µg recombinant HBsAg protein, adsorbed onto 0.25 mg aluminium hydroxide. ***Dialysis formulation*** – Each 1.0 mL monodose vial contains 40 µg recombinant HBsAg protein, adsorbed onto 0.5 mg aluminium hydroxide.
  All formulations may contain yeast proteins.

Combination vaccines that contain hepatitis B

- ***Hexaxim*** – Sanofi-Aventis Australia Pty Ltd (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b). Each 0.5 mL pre-filled syringe contains ≥20 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1), 32 D-antigen units type 3 (Saukett) and 12 µg purified Hib capsular polysaccharide (PRP) conjugated to 22–36 µg tetanus toxoid, adsorbed onto 0.6 mg aluminium as aluminium hydroxide. May contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B.
- ***Infanrix hexa*** – GlaxoSmithKline Australia Pty Ltd (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b). The vaccine consists of *both* a

0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg pertactin, 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.

- ***Twinrix Junior (360/10)*** – GlaxoSmithKline Australia Pty Ltd (formaldehyde-inactivated hepatitis A virus [HM175 strain] and recombinant hepatitis B vaccine). Each 0.5 mL monodose vial or pre-filled syringe contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface antigen protein; 0.225 mg aluminium as aluminium phosphate/hydroxide; traces of formaldehyde, neomycin, trometamol and polysorbate 20. May contain yeast proteins.
- ***Twinrix (720/20)*** – GlaxoSmithKline Australia Pty Ltd (formaldehyde-inactivated hepatitis A virus [HM175 strain] and recombinant hepatitis B vaccine). Each 1.0 mL monodose vial or pre-filled syringe contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein; 0.45 mg aluminium as aluminium phosphate/hydroxide; traces of formaldehyde, neomycin, trometamol and polysorbate 20. May contain yeast proteins.

Hepatitis B vaccines are prepared using recombinant technology. After purification, the HBsAg protein is adsorbed onto elemental aluminium (as hydroxide and/or phosphate). Hepatitis B vaccines may contain up to 1% yeast proteins (but no yeast DNA).

The Engerix-B and the H-B-Vax II vaccines are manufactured by different processes, and the HBsAg content of 'equivalent' doses of these two vaccines is different. The HBsAg content of the paediatric formulations of these two vaccines is half that of the corresponding manufacturer's adult formulation. Studies of hepatitis B vaccines have been conducted using different schedules and intervals for different age groups. Acceptable schedules are shown in Table 4.5.1 and are described below.

The standard 3-dose schedule and variations

Neonates, children and young adults aged <20 years

The recommended Australian infant schedule consists of a dose of monovalent hepatitis B vaccine given at birth, followed by 3 doses of a hepatitis B-containing combination vaccine, given at 2, 4 and 6 months of age (refer to 'Infants and young children' in 4.5.7 *Recommendations* below). If an infant did not receive the birth dose within the 1st 7 days of life, catch-up of that dose is *not* necessary. Such infants then only require 3 doses of a hepatitis B-containing vaccine, given at 2, 4 and 6 months of age.

A 3-dose schedule at birth, 1–2 months and 6–18 months of age has been shown to be equally as immunogenic as the recommended Australian schedule above; such schedules are often used overseas.[30-32] Children born overseas who have received hepatitis B vaccine in such a 3-dose schedule can also be considered to have completed the primary vaccination course.

For infants, the final dose of the primary hepatitis B vaccine course should preferably be administered at ≥24 weeks of age. However, if the final dose is given at <24 weeks but ≥16 weeks of age, it is not necessary to repeat the dose, provided the minimum intervals between doses in Table 2.1.7 (in 2.1.5 *Catch-up*) have been met.

For older children and young adults aged <20 years (who have not received hepatitis B vaccination earlier in life) a 3-dose schedule of the *paediatric* formulation (0.5 mL) of monovalent hepatitis B vaccine can be used (at times 0, 1 and 6 months), as per Table 4.5.1. Immunogenicity studies suggest there can be some flexibility of the vaccination schedule intervals for monovalent hepatitis B vaccines. The use of longer time intervals between doses does not impair the immunogenicity of hepatitis B vaccine.[33,34] The minimum interval between the 1st and 3rd doses of a 3-dose primary schedule is 4 months. This means that a shortened 3-dose schedule provided at either 0, 1, 4 months or 0, 2, 4 months is acceptable.[35] More compressed 3-dose schedules (e.g. 0, 1, 3 months) are not recommended. Such compressed schedules are associated with lower peak levels of anti-HBs antibody,[36,37] and hence likely shorter duration of antibody persistence (at levels ≥10 mIU/mL),[38] although the clinical significance of this is uncertain.[39] (Refer also to 'Adults aged ≥20 years' below.)

Adults aged ≥20 years

For adults, monovalent hepatitis B vaccine *adult* formulation (1.0 mL) is given in a 3-dose schedule at times 0, 1 and 6 months (refer to Table 4.5.1). There is some flexibility regarding the interval between the doses. The proportion of vaccine recipients attaining a seroprotective anti-HBs antibody level (≥10 mIU/mL), generally measured 1–2 months after vaccination, is comparable between adults who received their 3rd dose at 4–6 months after the 1st dose and those who received their 3rd dose 6 months or more after the 1st dose.[40] Increasing the interval between the 1st and 2nd doses has little effect on the final antibody level attained, but a longer interval between the 2nd and 3rd doses is associated

with a higher final antibody level.[37,41,42] However, for those who may be exposed to hepatitis B, delaying the 3rd dose may increase the risk of acquiring HBV infection.

For a shortened 3-dose schedule to attain comparable antibody levels to the standard 3-dose schedule, all three of the following minimum interval requirements must be satisfied:

- the *minimum interval* between the 1st and 2nd doses is 1 month,
- the *minimum interval* between the 2nd and 3rd doses is 2 months, and
- the *minimum interval* between the 1st and 3rd doses is 4 months.

That is, either a 0, 1, 4 month or a 0, 2, 4 month interval schedule is an acceptable 3-dose schedule for adults.[43]

The minimum intervals outlined above should be met where possible. More compressed 3-dose schedules (e.g. 0, 1, 3 months) are not recommended. If a compressed 3-dose schedule that does not meet these minimum intervals has already been administered, it may not be necessary to repeat a dose. Although compressed schedules are associated with lower peak antibody levels[41] and hence likely shorter duration of antibody levels ≥10 mIU/mL,[38] the significance of this is unclear. The majority of individuals in whom anti-HBs becomes undetectable have been shown to mount an anamnestic response to an additional vaccine dose, which indicates they are likely to be protected if exposed to hepatitis B virus.[39]

Note that the interval between the 1st and 3rd doses has been shortened to less than 4 months in studies of *4-dose* accelerated schedules, with the aim to achieve a higher seroprotective antibody level sooner. However, as antibody levels are substantially lower after 3 accelerated doses than after the standard 3-dose schedule,[42] a 4th dose is required to achieve comparable antibody levels to the standard 3-dose schedule (refer to 'Accelerated schedules' below).

The standard 3-dose schedule induces protective levels of neutralising antibody against hepatitis B virus in more than 90% of adults. The frequency of seroconversion increases progressively from approximately 35% after the 1st dose to more than 90% after the 3rd dose. There is evidence of immunity in most vaccine recipients after administration of 2 doses of a 3-dose schedule. However, the 3rd dose is necessary to increase the percentage of responders and to provide long-term protection.

Alternative 2-dose schedule for adolescents

Several studies have demonstrated that adolescents 11–15 years of age who receive 2 doses of adult formulation monovalent hepatitis B vaccine 4 to 6 months apart develop similar protective antibody levels to those vaccinated using paediatric formulations in the standard 3-dose schedule.[44-46]

Using a 2-dose schedule for the 11–15 years age group may improve compliance and will provide comparable immunogenicity to that of a 3-dose paediatric schedule. Adolescents (11–15 years of age) can be vaccinated with the adult formulation of either H-B-Vax II or Engerix-B in a 2-dose schedule (refer to Table 4.5.1).

Table 4.5.1: Recommended schedules for use of monovalent hepatitis B and hepatitis B combination vaccines

Vaccine	Age of vaccine recipient	Dose ($HBsAg$ protein)	Volume per dose (mL)	Number of doses	Recommended schedule intervals*†
Recommended infant schedule					
Engerix-B (paediatric formulation) or H-B-Vax II (paediatric formulation)	birth	10 µg (Engerix-B) or 5 µg (H-B-Vax II)	0.5	1	Birth (if not given at birth, may be given up to 7 days of age)
Combination hepatitis B-containing vaccine (e.g. Infanrix hexa DTPa-hepB-IPV-Hib)	2, 4 and 6‡ months	10 µg	0.5	3	1st dose: 2 months of age§ 2nd dose: 4 months of age (2 months after 1st dose) 3rd dose‡: 6 months of age (2 months after 2nd dose)

Vaccine	Age of vaccine recipient	Dose (HBsAg protein)	Volume per dose (mL)	Number of doses	Recommended schedule intervals*†
Monovalent hepatitis B vaccines – standard 3-dose schedule					
Engerix-B (paediatric formulation)	<20 years	10 µg	0.5	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Engerix-B (adult formulation)	≥20 years	20 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
H-B-Vax II (paediatric formulation)	<20 years	5 µg	0.5	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
H-B-Vax II (adult formulation)	≥20 years	10 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
H-B-Vax II (dialysis formulation)	≥20 years	40 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Monovalent hepatitis B vaccines – 2-dose schedule ONLY for adolescents aged 11–15 years					
Engerix-B (adult formulation)	11–15 years	20 µg	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 months after 1st dose
H-B-Vax II (adult formulation)	11–15 years	10 µg	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: between 4 and 6 months after 1st dose
Combination hepatitis A/hepatitis B vaccines					
Twinrix (720/20)¶	1–<16 years	20 µg	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: between 6 and 12 months after 1st dose (2-dose schedule)
Twinrix Junior (360/10)	1–<16 years	10 µg	0.5	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Twinrix (720/20)	≥16 years	20 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose

* For minimum intervals, refer to text above.

† In these schedules, the 'day 0' dose refers to the day when the 1st dose is given (i.e. day 0 of the vaccination course), not the age of the recipient. For infant vaccination, where the 1st dose is a 'birth dose' it is indicated as so.

‡ The final dose of the primary course for infants should preferably be given at ≥24 weeks of age; however, if given at <24 weeks but ≥16 weeks of age, it is not necessary to repeat the dose, provided the minimum intervals between doses have been met (refer to Table 2.1.7 in 2.1.5 *Catch-up*).

§ The 2 month dose can be given as early as 6 weeks of age.

¶ This schedule should not be used for those who require prompt protection against hepatitis B, for example, if there is close contact with a person known to be chronically infected with hepatitis B.

Accelerated schedules

Engerix-B (monovalent hepatitis B vaccine, paediatric and adult) and Twinrix (720/20) (combination hepatitis A/hepatitis B vaccine) are also registered for use in accelerated schedules, which consist of 4 doses in total (refer to Table 4.5.2). Accelerated schedules result in a high proportion of vaccine recipients attaining a seroprotective anti-HBs antibody level (≥10 mIU/mL) in the early months following commencement of the schedule. However, multiple studies have consistently shown that antibody levels are substantially lower at month 7, after 3 accelerated doses, than after the standard 3-dose schedule (0, 1, 6 months).[42] Also, some studies, in particular among persons who inject drugs and/or inmates of correctional facilities, have shown a lower proportion of subjects attaining the seroprotective antibody level after 3 doses of an accelerated schedule than after the standard 3-dose schedule.[42,47,48] After the 4th dose of an accelerated schedule, administered at 12 months, anti-HBs antibody levels are higher or comparable to those after a standard 3-dose schedule. Hence, a 4th dose should be administered at 12 months to complete an accelerated schedule.

Accelerated schedules should only be used for those persons with an imminent risk of exposure, such as those intending to travel to hepatitis B endemic areas with a very limited time before departure. As higher seroprotective rates after the 3rd dose of an accelerated 4-dose schedule are seen after the 0, 1, 2, 12 months schedule than after the 0, 7, 21 days, 12 months schedule, it is recommended that the latter schedule only be used in exceptional circumstances.

Table 4.5.2: Accelerated hepatitis B vaccination schedules (for persons with imminent risk of exposure)

Vaccine	Age of vaccine recipient (years)	Dose (HBsAg protein)	Volume (mL)	Number of doses	Recommended schedule minimum interval
Engerix-B (paediatric formulation)	<20	10 µg	0.5	4	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 2 months after 1st dose 4th dose: 12 months after 1st dose
Engerix-B (adult formulation)	≥20	20 µg	1.0	4	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 2 months after 1st dose 4th dose: 12 months after 1st dose or 1st dose: day 0 (day of vaccination) 2nd dose: 7 days after 1st dose 3rd dose: 21 days after 1st dose 4th dose: 12 months after 1st dose
Twinrix (720/20)	≥16	20 µg	1.0	4	1st dose: day 0 (day of vaccination) 2nd dose: 7 days after 1st dose 3rd dose: 21 days after 1st dose 4th dose: 12 months after 1st dose

Combination hepatitis A/hepatitis B vaccine schedules

The schedules for combination hepatitis A/hepatitis B vaccines are shown in Table 4.5.1 (and 4.4 *Hepatitis A*). Three-dose schedules for adults and children aged <16 years are acceptable; however, a 2-dose schedule in children 1–15 years of age, using Twinrix (720/20), also results in protective antibody levels for both hepatitis A and hepatitis B. An accelerated schedule for combination hepatitis A/hepatitis B vaccine in those aged ≥16 years is shown in Table 4.5.2. The appropriate use of accelerated schedules is discussed above.

The use of mixed vaccine schedules using both the combination hepatitis A/hepatitis B vaccine and monovalent hepatitis B vaccines is not routinely recommended. Generally, use of the same brand of vaccine is recommended. (Refer also to 'Interchangeability of hepatitis B vaccines' in 4.5.6 *Dosage and administration* below.)

4.5.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[49] Store at +2°C to +8°C. Do not freeze.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

4.5.6 Dosage and administration

The schedules for hepatitis B vaccines and for combination hepatitis A/hepatitis B vaccines are shown in Tables 4.5.1 and 4.5.2. For combination hepatitis A/hepatitis B vaccines, refer also to 4.4 *Hepatitis A*.

The dose of Engerix-B and H-B-Vax II (paediatric formulations) and Twinrix Junior (360/10) is 0.5 mL, to be given by IM injection.

The dose of Engerix-B and H-B-Vax II (adult formulations) and Twinrix (720/20) is 1.0 mL, to be given by IM injection.

The dose of Infanrix hexa is 0.5 mL, to be given by IM injection.

Hepatitis B and combination hepatitis A/hepatitis B vaccines can generally be co-administered simultaneously with, or at any time before or after, all other vaccines.

Interchangeability of hepatitis B vaccines

The Engerix-B and H-B-Vax II vaccines are manufactured by different processes, and the HBsAg content of an 'equivalent' dose is different. Although switching of vaccine brands is not recommended, in cases where the brand of vaccine used for previous doses is not known, another age-appropriate 'equivalent' dose brand (refer to Table 4.5.1) may be used. For example, a study in healthy neonates demonstrated comparable high levels of immunogenicity between two different mixed regimens that used two monovalent hepatitis B vaccines from different manufacturers.[50] As there is only one brand of combination hepatitis A/hepatitis B vaccine, interchangeability is not relevant. (Refer also to 'Combination hepatitis A/hepatitis B vaccine schedules' in 4.5.4 *Vaccines* above.)

4.5.7 Recommendations

Infants and young children

The recommended hepatitis B vaccine schedule for infants from birth is shown in Table 4.5.1. A birth dose of monovalent paediatric formulation hepatitis B vaccine is recommended for all newborn infants. Following this birth dose, 3 doses of a hepatitis-B-containing vaccine (usually provided as DTPa-hepB-IPV-Hib) are recommended for all children, at 2, 4 and 6 months of age. Thus, a total of 4 doses of hepatitis B vaccine are provided in the 1st year of life. The 1st dose of a hepatitis B-containing vaccine can be given as early as 6 weeks of age. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age.

If an infant has not received a birth dose within the 1st 7 days of life, a primary 3-dose course of a hepatitis B-containing combination vaccine should be given, at 2, 4 and 6 months of age; catch-up of the birth dose is *not* necessary.

The rationale for recommending the birth dose for all newborn infants is not only to prevent vertical transmission from a mother with chronic hepatitis B infection (recognising that there may be errors or delays in maternal testing, reporting, communication or appropriate response), but also to prevent horizontal transmission to the infant in the first months of life from persons with chronic hepatitis B infection who are household or other close contacts.[51] The birth dose should be given as soon as the baby is medically stable, and preferably within 24 hours of birth. Every effort should be made to administer the vaccine before discharge from the obstetric hospital or delivery unit. All newborns of mothers known to have chronic hepatitis B infection *must* be given a birth dose of hepatitis B vaccine *and* HBIG (refer to 'Management of infants born to mothers who are HBsAg-positive' below).

Although it is not routinely recommended in Australia, infants or toddlers who have received a 3-dose schedule of hepatitis B vaccine (often given overseas) with doses at birth, 1–2 months of age and ≥6 months of age can also be considered fully vaccinated (refer to 4.5.4 *Vaccines*, 'The standard 3-dose schedule and variations' above).

The final dose of the primary hepatitis B vaccine course in infants should preferably be administered at ≥24 weeks of age. However, if the final dose is given at <24 weeks but ≥16 weeks of age, it is not necessary to repeat the dose, provided the minimum intervals between doses in Table 2.1.7 (in 2.1.5 *Catch-up*) have been met.

Management of infants born to mothers who are HBsAg-positive

Routine antenatal screening of pregnant women for HBsAg is recommended to enable appropriate management to prevent newborn infants developing HBV infection (refer to 4.5.2 *Clinical features* and 4.5.3 *Epidemiology* above).[52-54]

It also enables appropriate follow-up and management of mothers who have chronic HBV infection, identification of the HBV immune status of other household members, and protection of those who are susceptible to HBV infection.

Infants born to HBsAg-positive mothers should be given HBIG and a dose of monovalent hepatitis B vaccine on the day of birth, concurrently but in separate thighs. The dose of HBIG is 100 IU, to be given by IM injection. It is preferable to administer HBIG immediately after birth (preferably within 12 hours of birth and certainly within 48 hours) as its efficacy decreases markedly if given more than 48 hours after birth.

The dose of monovalent hepatitis B vaccine should be given to the infant preferably within 24 hours of birth, and definitely within 7 days. This regimen results in seroconversion rates of more than 90% in neonates, even with concurrent administration of HBIG. Vaccination should not be delayed beyond 7 days after birth, as vaccination alone has been shown to be reasonably effective in preventing infection, provided it is given early.[55] Three subsequent doses of a hepatitis B-containing vaccine should be given, at 2, 4 and 6 months of age, so that the infant receives a total of 4 doses of hepatitis B-containing vaccines.

Anti-HBs antibody and HBsAg levels should be measured in infants born to mothers with chronic hepatitis B infection 3 to 12 months after completing the primary vaccine course. Testing should not be performed before 9 months of age to avoid detection of anti-HBs antibodies from HBIG given at birth. If anti-HBs antibody levels are adequate (≥10 mIU/mL) and HBsAg is negative, then the infant is considered to be protected[35] (refer to 'Serological testing following hepatitis B vaccination' below). If the anti-HBs level is <10 mIU/mL, expert advice regarding revaccination and/or further testing should be sought.

Preterm and low-birth-weight infants

Low-birth-weight preterm newborn infants do not respond as well to hepatitis B-containing vaccines as full-term infants.[56-58] Thus, for low-birth-weight infants (<2000 g) and/or infants born at <32 weeks gestation (irrespective of weight), it is recommended to give the vaccine in a 4-dose schedule at 0 (birth), 2, 4 and 6 months of age, followed by either:

- measuring the anti-HBs antibody level at 7 months of age, and if the antibody titre is <10 mIU/mL, giving a booster at 12 months of age (due to a better immunogenic response at this age compared with a younger age); or
- giving a booster of a hepatitis B-containing vaccine at 12 months of age (without measuring the antibody titre).

HIV-positive and immunocompromised children

All HIV-positive and immunocompromised children should be age-appropriately vaccinated against hepatitis B.

HIV-positive children should receive 3 doses of hepatitis B vaccine using an adult formulation (i.e. double the standard recommended dose for children). In a limited number of studies, paediatric haemodialysis patients have demonstrated improved response when given higher doses in a 3-dose schedule.[59,60]

For specific hepatitis B recommendations for immunocompromised children, refer to 3.3.3 *Vaccination of immunocompromised persons*.

Adolescents

Vaccination of adolescents 10–13 years of age is recommended for all those in this age group who have not already received a primary course of hepatitis B vaccine. Refer to your state/territory health authority for further information about hepatitis B vaccine for this age group (refer to Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

As the risk in Australian schools is very low,[61] vaccination of classroom contacts of hepatitis B cases is seldom indicated. Nevertheless, vaccination of all children and adolescents should be encouraged.

A 2-dose schedule of hepatitis B vaccine using the adult formulation of either of the available monovalent vaccines should be considered for adolescents aged 11–15 years who are to receive hepatitis B vaccination (refer to Table 4.5.1 and 4.5.4 *Vaccines* above). A 2-dose schedule increases compliance and thus protection in this age group.

Adolescents who did not receive an age-appropriate completed course of vaccination should be identified and offered catch-up vaccination, particularly if they fall into one of the risk categories for hepatitis B infection, discussed under 'Adults' below.

Adults

Hepatitis B vaccination is recommended for the following groups of adults because they are either at a higher risk of acquiring hepatitis B infection and/or at higher risk of severe disease. Refer to Table 4.5.1 and 4.5.4 *Vaccines* above for recommended adult vaccination schedules. Serological testing for previous or chronic hepatitis B infection may be indicated in many circumstances (refer to 'Serological testing prior to hepatitis B vaccination' below). Refer also to 3.3 *Groups with special vaccination requirements*.

When vaccination against both hepatitis B and hepatitis A is indicated, the combination hepatitis A/hepatitis B vaccines may be used. Refer to Tables 4.5.1 and 4.5.2 above and 'Recommendations for the use of combination hepatitis A/hepatitis B vaccines' below.

Household or other close (household-like) contacts of persons with hepatitis B

There is a low, but definite, risk of transmission from a person with acute or chronic hepatitis B to household or other close residential contacts (e.g. students or asylum seekers sharing residential facilities). This can be reduced by avoiding contact with blood or other body fluids and not sharing items that may penetrate the skin (such as combs, nail brushes, toothbrushes and razors). Immunisation of susceptible household-like contacts is strongly recommended. This includes household members of the adoptive family if the adopted child is known to have chronic hepatitis B infection.

Sexual contacts of persons with hepatitis B

Susceptible sexual partners of persons who are HBsAg-positive should be offered post-exposure HBIG and hepatitis B vaccination; both should be initiated within 14 days of the last sexual contact (refer to 4.5.11 *Public health management of hepatitis B* below and Table 4.5.3).

Hepatitis B is relatively common in clients of sexual health services and vaccination should be offered to susceptible persons at the time of first attendance.

Susceptible, sexually active men who have sex with men should be vaccinated. The combination hepatitis A/hepatitis B vaccine may be appropriate for men who have sex with men, if they are not immune to either disease, as they are at increased risk of both conditions (refer to 'Recommendations for the use of combination hepatitis A/hepatitis B vaccines' below).

Migrants from hepatitis B endemic countries

Migrants from hepatitis B endemic countries have a higher likelihood of having been previously infected with hepatitis B and of having a close household contact with chronic hepatitis B infection. Such persons should be offered testing for hepatitis B, and vaccination if appropriate. (Refer also to 3.3.8 *Vaccination of migrants to Australia*.) Areas of high endemicity, indicated by high seroprevalence of HBsAg, include most of East and Southeast Asia (except Japan), Pacific island groups, parts of central Asia and the Middle East, the Amazon Basin, and sub-Saharan Africa.[62]

Aboriginal and Torres Strait Islander people

There is an increased risk of acquiring new HBV infection among Aboriginal and Torres Strait Islander people compared with other Australians.[17,18] Although many younger Aboriginal and Torres Strait Islander people, especially children and adolescents, would have been eligible for, and have received, hepatitis B vaccination through population-wide vaccination programs, it is recommended that Aboriginal and Torres Strait Islander people have their risks and vaccination status for hepatitis B reviewed, be offered testing for previous hepatitis B infection, and be offered vaccination if non-immune. (Refer also to 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

Adult haemodialysis patients and patients with severely impaired renal function in whom dialysis is anticipated

Dialysis patients, and patients with severely impaired renal function in whom dialysis is anticipated, may be at increased risk of acquiring hepatitis B infection and also respond less well to vaccination. These patients should be given a larger than usual dose of hepatitis B vaccine.

Adult haemodialysis or pre-dialysis patients should be given either:

- 1.0 mL of Engerix-B adult formulation (20 µg) in each arm at each schedule point (i.e. effectively giving a double dose on each occasion) in a 4-dose schedule at 0, 1, 2 and 6 months;[63] or
- a single dose of H-B-Vax II dialysis formulation (40 µg) on each occasion in a 3-dose schedule at 0, 1 and 6 months.

Solid organ and haematopoietic stem cell transplant recipients

If seronegative for hepatitis B, solid organ transplant recipients should be vaccinated before transplantation as they may be at increased risk of infection from the transplanted organ.[64] Haematopoietic stem cell transplant recipients should be revaccinated following transplantation, due to the loss of immune memory that often follows the transplant procedure. (Refer also to 3.3.3 *Vaccination of immunocompromised persons*.)

HIV-positive adults and other immunocompromised adults

HIV-positive adults, and other immunocompromised adults, may be at increased risk of acquiring hepatitis B infection and also respond less well to vaccination. Limited studies in HIV1-positive adults have demonstrated an improved and accelerated serological response to a schedule that consists of 4 double doses, comprising two injections of the standard adult dose (using Engerix-B) on each occasion, at times 0, 1, 2 and 6 months.[65,66]

Persons with chronic liver disease and/or hepatitis C

Hepatitis B vaccination is recommended for those in this category who are seronegative for hepatitis B, because of the risk of severe liver disease following infection with hepatitis B.[67]

Persons who inject drugs

Persons who inject drugs should be tested, and be vaccinated if they have not previously been infected with HBV.

Recipients of certain blood products

Screening of all blood donors for HBV using HBsAg and nucleic acid amplification tests has greatly decreased the incidence of transfusion-related hepatitis B virus infection. Since 2010, nucleic acid testing has been introduced nationally to improve detection of hepatitis B infection in donated blood, mainly through reduction of the infectious window period when acute hepatitis B infection may not be detected using HBsAg, but also through detecting persons with occult hepatitis B infection. This further reduces the residual risk of hepatitis B transmission through transfusion in Australia to approximately 1 in 982 000 per unit transfused.[21] However, persons with clotting disorders who receive blood product concentrates, persons with recurrent transfusion requirements, and persons with underlying immunocompromise[68] have an elevated risk of hepatitis B virus infection, and should therefore be vaccinated.

Persons with developmental disabilities

Vaccination is recommended for persons who attend either residential or non-residential day-care facilities for persons with developmental disabilities. This is due to the high prevalence of markers indicating past or current infection in persons in these settings, including an HBsAg prevalence of >10%.[69-71]

Inmates of correctional facilities

Inmates are at increased risk of hepatitis B infection because of the prevalence of chronic hepatitis B among inmates, and the potential for unprotected sexual intercourse, injecting drug use and amateur tattooing in correctional facilities. Therefore, they should be offered the opportunity to be screened for hepatitis B upon incarceration, as part of the preventive health program for blood-borne viruses, and vaccinated if susceptible.

Sex industry workers

Sex industry workers are one of the population groups at higher risk of HBV infection. They have been specifically identified as an important population on which to focus for the prevention of hepatitis B transmission.[72] They are at a particularly high risk if they engage in unprotected sex.

Persons at occupational risk

The risk to persons in certain occupations differs considerably from setting to setting in different parts of Australia. However, it is recommended that all staff directly involved in patient care and/or the handling of human tissue, blood or body fluids should be vaccinated. In addition, standard precautions against exposure to human tissue, blood or body fluids should be used as a matter of routine.[73]

Other occupations where the risk of acquiring hepatitis B is increased include:

- police, members of the armed forces, emergency services staff and staff of correctional facilities; these persons should be vaccinated if they are assigned to duties that may involve exposure to human tissue, blood or body fluids
- funeral workers, embalmers and other workers who have regular contact with human tissue, blood or body fluids and/or used needles or syringes
- staff involved in both residential and non-residential care of persons with developmental disabilities, due to the high prevalence of markers of past or current infection in persons in this setting[69-71]
- workers who perform skin penetration procedures (e.g. tattooists, body-piercers).

Staff of child day-care centres will normally be at minimal risk of hepatitis B. If advice on risk is sought, the enquiry should be directed to the local public health authority.

Contact sports generally carry a low risk of hepatitis B infection. However, age-appropriate hepatitis B vaccination is recommended.

Travellers to hepatitis B endemic areas

Persons travelling to regions of intermediate or high endemicity, either long-term or for frequent short terms, or who are likely to undertake activities that increase their risks of exposure to HBV during travel, should be vaccinated.[62] (Refer also to 3.2 *Vaccination for international travel*.)

Recommendations for the use of combination hepatitis A/hepatitis B vaccines

Combination hepatitis A/hepatitis B vaccines should be considered for susceptible persons in whom both hepatitis A and hepatitis B vaccines are recommended, including:

- travellers to, and expatriates living in, moderately to highly endemic areas for hepatitis A and B
- persons whose lifestyle puts them at increased risk of hepatitis A and hepatitis B (sexually active men who have sex with men, sex industry workers, persons who inject drugs and inmates of correctional facilities)
- persons who attend or work at residential or non-residential facilities for people with developmental disabilities
- persons with occupational risks of exposure to both hepatitis A and hepatitis B
- persons with chronic liver disease and/or hepatitis C
- solid organ transplant liver recipients or solid organ transplant recipients who have chronic liver disease (refer to Table 3.3.2 *Recommendations for vaccinations for solid organ transplant (SOT) recipients*).

If a combination hepatitis A/hepatitis B vaccine is not available, monovalent hepatitis A and hepatitis B vaccines can be administered simultaneously (in separate syringes at separate sites) (refer to 'Interchangeability of hepatitis B vaccines' above).

Refer to 4.5.7 *Recommendations* above and 4.4 *Hepatitis A* for more details. Refer also to 3.3 *Groups with special vaccination requirements*.

Booster doses

Booster doses of hepatitis B vaccine (after completion of a primary course using a recommended schedule) are not recommended for immunocompetent persons. This applies to children and adults, including healthcare workers and dentists.[74-80] This is because there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection. Even though vaccine-induced antibody levels may decline with time and may become undetectable, immune memory persists and is thought to result in a protective immune response on re-exposure.[81] However, booster doses are recommended for persons who are immunocompromised, in particular those with either HIV infection or renal failure. The time for boosting in such persons should be decided by regular monitoring of anti-HBs levels at 6- to 12-monthly intervals.[74]

Serological testing prior to hepatitis B vaccination

Routine antenatal screening of all pregnant women for HBsAg is recommended to allow appropriate measures to be implemented to prevent newborn infants developing chronic HBV infection[52-54] (refer to 'Management of infants born to mothers who are HBsAg-positive' above).

Serological testing for evidence of past (or current) hepatitis B infection prior to vaccination may be warranted for certain older children, adolescents and adults. This is particularly so for those at increased risk of acquiring hepatitis B infection, such as persons who inject drugs, sex industry workers, immunocompromised persons, and those living in communities with higher prevalence of HBV, including migrant communities and Aboriginal and Torres Strait Islander people. Serological testing enables identification of persons who were infected by HBV, to facilitate timely appropriate clinical management and prevention of onward transmission, hence reducing population impact of HBV infection. Testing also identifies those who are susceptible to HBV infection and, as such, should be offered vaccination if they continue to have a high exposure risk (refer to 4.5.7 *Recommendations* above).[72] Testing for immunity to hepatitis A infection (and vaccination of susceptible at-risk persons with combination hepatitis A/hepatitis B vaccines) may also be indicated for some population groups at increased risk of hepatitis A exposure (refer to 4.4 *Hepatitis A*).

Interpretation of the results of serological testing may be enhanced by discussion with the laboratory that performed the test, ensuring that relevant clinical information is provided.

Serological testing following hepatitis B vaccination

Anti-HBs antibody and HBsAg levels should be measured in infants born to mothers with chronic hepatitis B infection 3 to 12 months after completing the primary vaccine course (for more information refer to 'Management of infants born to mothers who are HBsAg-positive' above).

Other than for infants born to mothers with chronic hepatitis B infection, post-vaccination serological testing is recommended 4 to 8 weeks after completion of the primary course for persons in the following categories:

- those at significant occupational risk (e.g. healthcare workers whose work involves frequent exposure to human tissue, blood or body fluids)
- those at risk of severe or complicated HBV disease (e.g. persons who are immunocompromised, and persons with pre-existing liver disease not related to hepatitis B)

- those in whom a poor response to hepatitis B vaccination may occur (e.g. haemodialysis patients, persons with bleeding disorders vaccinated via the SC route)
- sexual partners and household, or other close household-like, contacts of persons who are infected with hepatitis B.[35]

For these individuals, if adequate anti-HBs levels (≥10 mIU/mL) are not reached on serological testing 4 to 8 weeks after the 3rd dose, the possibility of HBV infection, including chronic HBV infection, should be investigated by testing for serological markers, including HBsAg and anti-HBc antibodies. In select cases in which hepatitis B infection is suspected, HBV nucleic acid testing may also be indicated, and expert advice regarding further management should be sought. If there are no markers of HBV infection, the individual should be managed as a non-responder to hepatitis B vaccination (refer to 'Non-responders to primary vaccination' below).

If persons who are at significant risk of hepatitis B (such as healthcare workers) were not tested for anti-HBs within 4 to 8 weeks after completion of the documented primary course, they should still undergo serological testing to ensure immunity. If, on testing, they have an anti-HBs level of <10 mIU/mL, they should be given a single booster dose (4th dose) of vaccine. Persons with immune memory established from effective prior vaccination should respond to this booster dose. Anti-HBs should be checked 4 weeks later, and if the anti-HBs level remains <10 mIU/mL, the possibility of HBV infection should be investigated (and, if excluded, the person should be managed as a non-responder to vaccination, refer below). If the anti-HBs level is ≥10 mIU/mL, the person can be regarded as immune.

Non-responders to primary vaccination

A non-responder is a person without HBV infection who has a documented history of an age-appropriate primary course of hepatitis B vaccine, but with a current anti-HBs level <10 mIU/mL. There are a number of potential options for non-responders. Persons who do not respond to the primary vaccination course, and in whom chronic HBV infection has been excluded, should be offered further doses.

As discussed above, in 'Serological testing following hepatitis B vaccination', a single booster dose (4th dose) of vaccine can be given to confirm non-responder status. Persons who are non-responders after being given the booster/4th dose (and in whom HBV infection has been excluded) should have 2 further doses of hepatitis B vaccine at monthly intervals, and be re-tested for anti-HBs levels at least 4 weeks after the last dose. The booster/4th dose that was received could be counted as the 1st of the 3 repeat doses, as recommended for non-responders. A few small studies have reported attainment of seroprotection in non-responders with high-dose formulations or double-dose administration for a 4th, or subsequent, dose of hepatitis B vaccination, but there is no consistent evidence to suggest that a higher proportion of subjects would respond with these higher-dose regimens.[82-84]

For HBsAg-negative healthcare workers who are non-responders to a primary course of vaccination and to subsequent additional IM doses (≥5 doses in total), some small observational studies report that some individuals may respond to the vaccine administered intradermally.[85-87] Engerix-B (0.25 mL [5 µg] per dose) was used in these studies, giving up to 4 doses.[85] Younger age and longer duration (≥6 months) since the last IM dose may be associated with greater probability of response.[86] If an intradermal dose(s) is given, it is recommended that the anti-HBs levels be measured before each subsequent dose to assess for seroconversion.

Persistent non-responders should be informed that they should be considered not protected against hepatitis B and should minimise exposures. They should also be informed about the need for HBIG within 72 hours of parenteral or mucosal exposure to HBV (refer to Table 4.5.3).

4.5.8 Pregnancy and breastfeeding

Hepatitis B vaccine is not routinely recommended for pregnant or breastfeeding women. However, the WHO states that neither pregnancy nor breastfeeding is a contraindication to the use of this vaccine.[88]

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.5.9 Contraindications

The only absolute contraindications to hepatitis B vaccines are:

- anaphylaxis following a previous dose of any hepatitis B vaccine
- anaphylaxis following any vaccine component.

In particular, hepatitis B vaccines are contraindicated in persons with a history of anaphylaxis to yeast.

4.5.10 Adverse events

Extensive experience indicates that the birth dose of hepatitis B vaccine is very well tolerated by newborn infants. It does not interfere with either the establishment or maintenance of breastfeeding, and it is not associated with an increased risk of either fever, medical investigation for sepsis, or serious outcomes in newborns who were vaccinated compared with the unvaccinated.[89-91]

Adverse events after hepatitis B vaccination are transient and minor, and include soreness at the injection site (5%), fever (usually low grade; 2–3%), nausea, dizziness, malaise, myalgia and arthralgia. Fever can be expected in some neonates following immunisation with hepatitis B vaccine (0.6–3.7%).

Anaphylaxis has been reported very rarely in adults, notably in yeast-sensitive individuals.[92] Although various adverse events such as demyelinating diseases, Guillain-Barré syndrome and arthritis have been reported, there is no evidence of a causal relationship with hepatitis B vaccination.[92,93]

The World Health Organization Global Advisory Committee on Vaccine Safety states that 'multiple studies and review panels have concluded that there is no link between MS [multiple sclerosis] and hepatitis B vaccination'.[94,95]

The vaccine produces neither therapeutic effects nor adverse events in persons with chronic HBV infection. It is also safe, though of no additional benefit, in those already immune to hepatitis B through past natural infection.

4.5.11 Public health management of hepatitis B

Acute hepatitis B and newly identified chronic hepatitis B are notifiable diseases in all states and territories in Australia.

Further instructions about the public health management of hepatitis B, including management of cases of acute hepatitis B and newly identified chronic hepatitis B, and their contacts, should be obtained from state/territory public health authorities (refer to Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Following significant exposure (percutaneous, ocular or mucous membrane) to blood or to potentially blood-contaminated secretions, where feasible, the source individual should be tested for HBsAg as soon as possible.

If the person exposed has not been previously vaccinated against hepatitis B, their anti-HBs level, and anti-HBc and HBsAg status, should be determined immediately. If the person exposed is anti-HBs and anti-HBc negative (non-immune) and the source is either HBsAg-positive or cannot be identified and tested rapidly, a single dose of HBIG should be administered according to the recommendations in Table 4.5.3. The dose of HBIG is 100 IU for children weighing up to 30 kg (about 5 years of age) and 400 IU for all others. Hepatitis B vaccine must also be given as soon as possible, with further doses as recommended in Table 4.5.3.

For previously vaccinated persons exposed to either an HBsAg-positive source or a source whose hepatitis B status cannot be determined, post-exposure prophylaxis is not necessary if there was a documented protective response (anti-HBs level ≥10 mIU/mL) at any time after vaccination. If the response to previous vaccination is unknown, the anti-HBs level should be determined as quickly as possible. If the anti-HBs level is <10 mIU/mL and there is no evidence of HBV infection, HBIG and HBV vaccine should be administered as per Table 4.5.3.

All healthcare workers should be immunised against hepatitis B. Completion of a full course of hepatitis B vaccination is strongly recommended for any non-immune healthcare worker who has sustained a needle-stick injury or other potential hepatitis B exposure.

Table 4.5.3: Post-exposure prophylaxis for non-immune persons exposed to a HBsAg-positive source

Type of exposure	Hepatitis B immunoglobulin		Vaccine	
Perinatal (exposure of babies during and after birth)*	100 IU, by IM injection	Single dose immediately after birth (preferably within 12 hours of birth and certainly within 48 hours)	0.5 mL, by IM injection	Immediately after birth (preferably within 24 hours, no later than 7 days),† then at 2, 4 and 6 months of age
Percutaneous, ocular or mucous membrane	400 IU, by IM injection 100 IU, if body weight <30 kg	Single dose within 72 hours of exposure	0.5 mL or 1 mL (depending on age), by IM injection	Within 7 days† of exposure and at 1 and 6 months after 1st dose
Sexual	400 IU, by IM injection 100 IU, if body weight <30 kg	Single dose, preferably within 72 hours of last sexual contact‡	0.5 mL or 1 mL (depending on age), by IM injection	Within 14 days† and at 1 and 6 months after 1st dose

* Refer also to 'Management of infants born to mothers who are HBsAg-positive' above.

† The 1st dose can be given at the same time as HBIG, but should be administered at a separate site. Administration as soon as possible after exposure is preferred.

‡ There is limited evidence for efficacy if given within 14 days of contact; however, administration as soon as possible after exposure is preferred.

- ***Hepatitis B Immunoglobulin-VF*** – CSL Limited. 160 mg/mL immunoglobulin (mainly IgG) prepared from human plasma containing high levels of antibody to surface antigen of the hepatitis B virus. Single vials contain 100 IU or 400 IU hepatitis B antibody, with the actual volume stated on the label on the vial. Also contains glycine.

Hepatitis B immunoglobulin (HBIG) is prepared from plasma donated through routine blood bank collection. Samples are selected on the basis that they contain high levels of anti-HBs antibodies. As stocks of HBIG are very limited, use should be strictly reserved for those who are at high risk, such as babies born to mothers with chronic HBV infection and non-immune persons who are exposed through occupational exposure to the blood of unidentified persons or to persons who are chronically infected with hepatitis B or whose hepatitis status cannot be ascertained in time.[88] Requests should be directed to the Australian Red Cross Blood Service in your state/territory (refer to 5.1.1 *Availability of immunoglobulins* in Part 5 *Passive immunisation*).

4.5.12 Variations from product information

The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and as a booster dose for children 18 months of age if boosting is required for all antigens. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix hexa states that this vaccine is contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au.

1. Mast EE, Ward JW. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines.* 5th ed. Philadelphia, PA: Saunders Elsevier, 2008.
2. Dandri M, Locarnini S. New insight in the pathobiology of hepatitis B virus infection. *Gut* 2012;61 Suppl 1:i6-17.
3. Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiologic Reviews* 2006;28:112-25.
4. McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *Journal of Infectious Diseases* 1985;151:599-603.
5. Koziel MJ, Thio CL. Hepatitis B virus and hepatitis delta virus. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases.* 7th ed. Philadelphia: Churchill Livingstone, 2010.
6. Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. *Proceedings of the Royal Society of London Series B: Biological Sciences* 1993;253:197-201.
7. Wood N, Backhouse J, Gidding HF, et al. Estimates of chronic hepatitis B virus infection in the Northern Territory. *Communicable Diseases Intelligence* 2005;29:289-90.
8. Clements CJ, Baoping Y, Crouch A, et al. Progress in the control of hepatitis B infection in the Western Pacific Region. *Vaccine* 2006;24:1975-82.
9. Wasley A, Kruszon-Moran D, Kuhnert W, et al. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. *Journal of Infectious Diseases* 2010;202:192-201.
10. Gidding HF, Warlow M, MacIntyre CR, et al. The impact of a new universal infant and school-based adolescent hepatitis B vaccination program in Australia. *Vaccine* 2007;25:8637-41.
11. Nguyen VT, Razali K, Amin J, Law MG, Dore GJ. Estimates and projections of hepatitis B-related hepatocellular carcinoma in Australia among people born in Asia-Pacific countries. *Journal of Gastroenterology and Hepatology* 2008;23:922-9.
12. O'Sullivan BG, Gidding HF, Law M, et al. Estimates of chronic hepatitis B virus infection in Australia, 2000. *Australian and New Zealand Journal of Public Health* 2004;28:212-6.
13. Tawk HM, Vickery K, Bisset L, et al. The current pattern of hepatitis B virus infection in Australia. *Journal of Viral Hepatitis* 2006;13:206-15.
14. The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2011. Sydney: The Kirby Institute, the University of New South Wales, 2011. Available at: kirby.unsw.edu.au/surveillance/Annual-Surveillance-Reports (accessed May 2012).
15. NNDSS Annual Report Writing Group. Australia's notifiable disease status, 2010: annual report of the National Notifiable Diseases Surveillance System. *Communicable Diseases Intelligence* 2012;36:1-69.
16. Chiu C, Dey A, Wang H, et al. Vaccine preventable diseases in Australia, 2005 to 2007. *Communicable Diseases Intelligence* 2010;34 Suppl:ix-S167.
17. Menzies R, Turnour C, Chiu C, McIntyre P. Vaccine preventable diseases and vaccination coverage in Aboriginal and Torres Strait Islander people, Australia, 2003 to 2006. *Communicable Diseases Intelligence* 2008;32 Suppl:S2-67.
18. The Kirby Institute. Bloodborne viral and sexually transmitted infections in Aboriginal and Torres Strait Islander people: surveillance and evaluation report 2011. Sydney: The Kirby Institute, the University of New South Wales, 2011. Available at: kirby.unsw.edu.au/surveillance/Aboriginal-Surveillance-Reports (accessed Sep 2012).
19. Reilly ML, Schillie SF, Smith E, et al. Increased risk of acute hepatitis B among adults with diagnosed diabetes mellitus. *Journal of Diabetes Science and Technology* 2012;6:858-66.
20. Seed CR, Kiely P, Keller AJ. Residual risk of transfusion transmitted human immunodeficiency virus, hepatitis B virus, hepatitis C virus and human T lymphotrophic virus. *Internal Medicine Journal* 2005;35:592-8.

21. Seed CR, Kiely P. A method for estimating the residual risk of transfusion-transmitted HBV infection associated with occult hepatitis B virus infection in a donor population without universal anti-HBc screening. *Vox Sanguinis* 2013;105:290-8.

22. van der Eijk AA, Niesters HG, Hansen BE, et al. Paired, quantitative measurements of hepatitis B virus DNA in saliva, urine and serum of chronic hepatitis B patients. *European Journal of Gastroenterology and Hepatology* 2005;17:1173-9.

23. Scott RM, Snitbhan R, Bancroft WH, Alter HJ, Tingpalapong M. Experimental transmission of hepatitis B virus by semen and saliva. *Journal of Infectious Diseases* 1980;142:67-71.

24. Marie-Cardine A, Mouterde O, Dubuisson S, Buffet-Janvresse C, Mallet E. Salivary transmission in an intrafamilial cluster of hepatitis B. *Journal of Pediatric Gastroenterology and Nutrition* 2002;34:227-30.

25. Alter HJ, Purcell RH, Gerin JL, et al. Transmission of hepatitis B to chimpanzees by hepatitis B surface antigen-positive saliva and semen. *Infection and Immunity* 1977;16:928-33.

26. Villarejos VM, Visoná KA, Gutiérrez A, Rodríguez A. Role of saliva, urine and feces in the transmission of type B hepatitis. *New England Journal of Medicine* 1974;291:1375-8.

27. Powell E, Duke M, Cooksley WG. Hepatitis B transmission within families: potential importance of saliva as a vehicle of spread. *Australian and New Zealand Journal of Medicine* 1985;15:717-20.

28. Hui AY, Hung LC, Tse PC, et al. Transmission of hepatitis B by human bite—confirmation by detection of virus in saliva and full genome sequencing. *Journal of Clinical Virology* 2005;33:254-6.

29. Bancroft WH, Snitbhan R, Scott RM, et al. Transmission of hepatitis B virus to gibbons by exposure to human saliva containing hepatitis B surface antigen. *Journal of Infectious Diseases* 1977;135:79-85.

30. Greenberg DP, Vadheim CM, Marcy SM, et al. Safety and immunogenicity of a recombinant hepatitis B vaccine administered to infants at 2, 4 and 6 months of age. *Vaccine* 1996;14:811-6.

31. Greenberg DP, Vadheim CM, Wong VK, et al. Comparative safety and immunogenicity of two recombinant hepatitis B vaccines given to infants at two, four and six months of age. *Pediatric Infectious Disease Journal* 1996;15:590-6.

32. Greenberg DP, Wong VK, Partridge S, Howe BJ, Ward JI. Safety and immunogenicity of a combination diphtheria-tetanus toxoids-acellular pertussis-hepatitis B vaccine administered at two, four and six months of age compared with monovalent hepatitis B vaccine administered at birth, one month and six months of age. *Pediatric Infectious Disease Journal* 2002;21:769-76.

33. André FE, Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. *Journal of Medical Virology* 1994;44:144-51.

34. Wiström J, Ahlm C, Lundberg S, Settergren B, Tärnvik A. Booster vaccination with recombinant hepatitis B vaccine four years after priming with one single dose. *Vaccine* 1999;17:2162-5.

35. Centers for Disease Control and Prevention (CDC), Mast EE, Margolis HS, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: immunization of infants, children, and adolescents. [errata appear in MMWR Morb Mortal Wkly Rep. 2006 Feb 17;55(6):158-9 and MMWR Morb Mortal Wkly Rep. 2007 Dec 7;56(48):1267]. *MMWR Recommendations and Reports* 2005;54(RR-16):1-32.

36. Mintai Z, Kezhou L, Lieming D, Smego RA, Jr. Duration and efficacy of immune response to hepatitis B vaccine in high-risk Chinese adolescents. *Clinical Infectious Diseases* 1993;16:165-7.

37. Hadler SC, de Monzon MA, Lugo DR, Perez M. Effect of timing of hepatitis B vaccine doses on response to vaccine in Yucpa Indians. *Vaccine* 1989;7:106-10.

38. Floreani A, Baldo V, Cristofoletti M, et al. Long-term persistence of anti-HBs after vaccination against HBV: an 18 year experience in health care workers. *Vaccine* 2004;22:607-10.

39. Schönberger K, Riedel C, Rückinger S, et al. Determinants of long-term protection after hepatitis B vaccination in infancy: a meta-analysis. *Pediatric Infectious Disease Journal* 2013;32:307-13.

40. Wouters K, Leuridan E, Van Herck K, et al. Compliance and immunogenicity of two hepatitis B vaccination schedules in sex workers in Belgium. *Vaccine* 2007;25:1893-900.

41. Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. *Journal of Infectious Diseases* 1989;160:766-9.

42. Van Herck K, Leuridan E, Van Damme P. Schedules for hepatitis B vaccination of risk groups: balancing immunogenicity and compliance. *Sexually Transmitted Infections* 2007;83:426-32.

43. Centers for Disease Control and Prevention (CDC), Mast EE, Weinbaum CM, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults. [erratum appears in MMWR Morb Mortal Wkly Rep. 2007 Oct 26;56(42):1114]. *MMWR Recommendations and Reports* 2006;55(RR-16):1-33.

44. Cassidy WM, Watson B, Ioli VA, et al. A randomized trial of alternative two- and three-dose hepatitis B vaccination regimens in adolescents: antibody responses, safety, and immunologic memory. *Pediatrics* 2001;107:626-31.

45. Heron L, Selnikova O, Moiseieva A, et al. Immunogenicity, reactogenicity and safety of two-dose versus three-dose (standard care) hepatitis B immunisation of healthy adolescents aged 11–15 years: a randomised controlled trial. *Vaccine* 2007;25:2817-22.

46. Van Damme P, Moiseeva A, Marichev I, et al. Five years follow-up following two or three doses of a hepatitis B vaccine in adolescents aged 11–15 years: a randomised controlled study. *BMC Infectious Diseases* 2010;10:357.

47. Quaglio G, Talamini G, Lugoboni F, et al. Compliance with hepatitis B vaccination in 1175 heroin users and risk factors associated with lack of vaccine response. *Addiction* 2002;97:985-92.

48. Christensen PB, Fisker N, Krarup HB, et al. Hepatitis B vaccination in prison with a 3-week schedule is more efficient than the standard 6-month schedule. *Vaccine* 2004;22:3897-901.

49. National vaccine storage guidelines: Strive for 5. 2nd ed. Canberra: Australian Government Department of Health and Ageing, 2013. Available at: www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/IMM77-cnt (accessed Nov 2013).

50. Seto D, West DJ, Gilliam RR, et al. Antibody responses of healthy neonates to two mixed regimens of hepatitis B vaccine. *Pediatric Infectious Disease Journal* 1999;18:840-2.

51. MacIntyre CR. Hepatitis B vaccine: risks and benefits of universal neonatal vaccination. *Journal of Paediatrics and Child Health* 2001;37:215-7.

52. Palasanthiran P, Starr M, Jones C, Giles M, eds. Management of perinatal infections. Sydney: Australasian Society for Infectious Diseases, 2014.

53. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Management of hepatitis B in pregnancy (C-Obs 50). 2013. Available at: www.ranzcog.edu.au/college-statements-guidelines.html (accessed Apr 2015).

54. National Hepatitis B Virus (HBV) Testing Policy Expert Reference Committee. National hepatitis B testing policy. 2014. Available at: testingportal.ashm.org.au/hbv (accessed Apr 2015).

55. Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. *BMJ* 2006;332:328-36.

56. Blondheim O, Bader D, Abend M, et al. Immunogenicity of hepatitis B vaccine in preterm infants. *Archives of Disease in Childhood Fetal and Neonatal Edition* 1998;79:F206-8.

57. Gołębiowska M, Kardas-Sobantka D, Chlebna-Sokół D, Sabanty W. Hepatitis B vaccination in preterm infants. *European Journal of Pediatrics* 1999;158:293-7.

58. Saari TN, American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. *Pediatrics* 2003;112:193-8.

59. Drachman R, Isacsohn M, Rudensky B, Drukker A. Vaccination against hepatitis B in children and adolescent patients on dialysis. *Nephrology Dialysis Transplantation* 1989;4:372-4.

60. Watkins SL, Alexander SR, Brewer ED, et al. Response to recombinant hepatitis B vaccine in children and adolescents with chronic renal failure. *American Journal of Kidney Diseases* 2002;40:365-72.

61. Gill JS, Bucens M, Hatton M, Carey M, Quadros CF. Markers of hepatitis B virus infection in schoolchildren in the Kimberley, Western Australia. *Medical Journal of Australia* 1990;153:34-7.

62. Averhoff F. Infectious diseases related to travel. Hepatitis B. In: *CDC Health information for international travel 2014: the Yellow Book.* New York: Oxford University Press, 2014. Available at: wwwnc.cdc.gov/travel (accessed Mar 2015).

63. El-Reshaid K, Al-Mufti S, Johny KV, Sugathan TN. Comparison of two immunization schedules with recombinant hepatitis B vaccine and natural immunity acquired by hepatitis B infection in dialysis patients. *Vaccine* 1994;12:223-34.

64. Danzinger-Isakov L, Kumar D, AST Infectious Diseases Community of Practice. Guidelines for vaccination of solid organ transplant candidates and recipients. *American Journal of Transplantation* 2009;9 Suppl 4:S258-62.

65. Potsch DV, Oliveira ML, Ginuíno C, et al. High rates of serological response to a modified hepatitis B vaccination schedule in HIV-infected adults subjects. *Vaccine* 2010;28:1447-50.

66. Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA* 2011;305:1432-40.

67. Chlabicz S, Grzeszczuk A. Hepatitis B virus vaccine for patients with hepatitis C virus infection. *Infection* 2000;28:341-5.

68. Candotti D, Allain JP. Transfusion-transmitted hepatitis B virus infection. *Journal of Hepatology* 2009;51:798-809.

69. Perrillo RP, Storch GA, Bodicky CJ, Campbell CR, Sanders GE. Survey of hepatitis B viral markers at a public day school and a residential institution sharing mentally handicapped students. *Journal of Infectious Diseases* 1984;149:796-800.

70. Perrillo RP, Strang S, Lowry OH. Different operating conditions affect risk of hepatitis B virus infection at two residential institutions for the mentally disabled. *American Journal of Epidemiology* 1986;123:690-8.

71. Woodruff BA, Vazquez E. Prevalence of hepatitis virus infections in an institution for persons with developmental disabilities. *American Journal of Mental Retardation* 2002;107:278-92.

72. Australian Government Department of Health and Ageing. National hepatitis B strategy 2010–2013. Canberra: Australian Government Department of Health and Ageing, 2010. Available at: www.health.gov.au/internet/main/publishing.nsf/Content/ohp-national-strategies-2010-hepb/$File/hepb.pdf (accessed Sep 2012).

73. Chen W, Gluud C. Vaccines for preventing hepatitis B in health-care workers. *Cochrane Database of Systematic Reviews* 2005;(4):CD000100. doi:10.1002/14651858.CD000100.pub3.

74. European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *The Lancet* 2000;355:561-5.

75. Williams JL, Christensen CJ, McMahon BJ, et al. Evaluation of the response to a booster dose of hepatitis B vaccine in previously immunized healthcare workers. *Vaccine* 2001;19:4081-5.

76. Watson B, West DJ, Chilkatowsky A, Piercy S, Ioli VA. Persistence of immunologic memory for 13 years in recipients of a recombinant hepatitis B vaccine. *Vaccine* 2001;19:3164-8.

77. Greub G, Zysset F, Genton B, Spertini F, Frei PC. Absence of anti-hepatitis B surface antibody after vaccination does not necessarily mean absence of immune response. *Medical Microbiology and Immunology* 2001;189:165-8.

78. Zanetti AR, Mariano A, Romanò L, et al. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. *The Lancet* 2005;366:1379-84.

79. FitzSimons D, François G, Hall A, et al. Long-term efficacy of hepatitis B vaccine, booster policy, and impact of hepatitis B virus mutants. *Vaccine* 2005;23:4158-66.

80. Petersen KM, Bulkow LR, McMahon BJ, et al. Duration of hepatitis B immunity in low risk children receiving hepatitis B vaccinations from birth. *Pediatric Infectious Disease Journal* 2004;23:650-5.

81. But DY, Lai CL, Lim WL, et al. Twenty-two years follow-up of a prospective randomized trial of hepatitis B vaccines without booster dose in children: final report. *Vaccine* 2008;26:6587-91.

82. Goldwater PN. Randomized, comparative trial of 20 μg vs 40 μg Engerix B vaccine in hepatitis B vaccine non-responders. *Vaccine* 1997;15:353-6.

83. Bertino JS, Jr., Tirrell P, Greenberg RN, et al. A comparative trial of standard or high-dose S subunit recombinant hepatitis B vaccine versus a vaccine containing S subunit, pre-S_1, and pre-S_2 particles for revaccination of healthy adult nonresponders. *Journal of Infectious Diseases* 1997;175:678-81.

84. Kim MJ, Nafziger AN, Harro CD, et al. Revaccination of healthy nonresponders with hepatitis B vaccine and prediction of seroprotection response. *Vaccine* 2003;21:1174-9.

85. Playford EG, Hogan PG, Bansal AS, et al. Intradermal recombinant hepatitis B vaccine for healthcare workers who fail to respond to intramuscular vaccine. *Infection Control and Hospital Epidemiology* 2002;23:87-90.

86. Ghebrehewet S, Baxter D, Falconer M, Paver K. Intradermal recombinant hepatitis B vaccination (IDRV) for non-responsive healthcare workers (HCWs). *Human Vaccines* 2008;4:280-5.

87. Roukens AH, Vossen AC, Boland GJ, et al. Intradermal hepatitis B vaccination in non-responders after topical application of imiquimod (Aldara®). *Vaccine* 2010;28:4288-93.

88. World Health Organization (WHO). Hepatitis B vaccines: WHO position paper. *Weekly Epidemiological Record* 2009;84:405-19.

89. Lewis E, Shinefield HR, Woodruff BA, et al. Safety of neonatal hepatitis B vaccine administration. *Pediatric Infectious Disease Journal* 2001;20:1049-54.

90. Niu MT, Salive ME, Ellenberg SS. Neonatal deaths after hepatitis B vaccine: the Vaccine Adverse Event Reporting System, 1991–1998. *Archives of Pediatrics and Adolescent Medicine* 1999;153:1279-82.

91. Eriksen EM, Perlman JA, Miller A, et al. Lack of association between hepatitis B birth immunization and neonatal death: a population-based study from the Vaccine Safety Datalink Project. *Pediatric Infectious Disease Journal* 2004;23:656-61.

92. Institute of Medicine. Stratton K, Ford A, Rusch E, Wright Clayton E, eds. *Adverse effects of vaccines: evidence and causality*. Washington, D.C.: The National Academies Press, 2012.

93. Duclos P. Safety of immunisation and adverse events following vaccination against hepatitis B. *Expert Opinion on Drug Safety* 2003;2:225-31.

94. World Health Organization (WHO). The Global Advisory Committee on Vaccine Safety rejects association between hepatitis B vaccination and multiple sclerosis (MS). 2002. Available at: www.who.int/vaccine_safety/committee/topics/hepatitisb/ms/en/ (accessed Mar 2015).

95. Zuckerman JN. Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines. *Journal of Medical Virology* 2006;78:169-77.