4.4 HEPATITIS A

4.4.1 Virology

Hepatitis A is an acute infection of the liver caused by the hepatitis A virus (HAV), a picornavirus (a small single-stranded RNA virus).[1] The virus survives well in the environment outside of the human host. It persists on hands for several hours and in food kept at room temperature for considerably longer, and is relatively resistant to heat and freezing.

4.4.2 Clinical features

Hepatitis A is an infection of humans; there is no animal reservoir.[1] HAV is predominantly transmitted by the faecal–oral route. The infecting dose is unknown, but it is presumed to be low. The incubation period of hepatitis A is 15 to 50 days, with a mean of about 28 days.[2] HAV is excreted in faeces for up to 2 weeks before the onset of illness and for at least 1 week afterwards.[1]

In young children, HAV usually causes either an asymptomatic infection or a very mild illness without jaundice; adults are more likely to have symptomatic infection (over 70%).[2] Patients with symptomatic illness typically have a 4- to 10-day prodrome of systemic (fever, malaise, weakness and anorexia) and gastrointestinal (nausea and vomiting) symptoms. Dark urine is usually the first specific manifestation of acute hepatitis A infection, followed a day or two later by jaundice and pale faeces.[2] The prodromal symptoms tend to wane with the onset of jaundice, although the anorexia and malaise may persist; pruritus and localised hepatic discomfort or pain may follow.[1] The duration of illness varies, but most patients feel better and have normal, or near normal, liver function tests within a month of the onset of illness.[3] Complications of hepatitis A are uncommon but include, on rare occasions, fulminant hepatitis.[4] The case-fatality rate of hepatitis A increases with age.[2] Hepatitis A does not cause chronic liver disease. Relapse has been found in up to 10% of cases, but recovery is universal. HAV does not cause chronic infection and immunity after infection is life-long.[2] Diagnosis of hepatitis A is made by detecting anti-HAV IgM in serum during the acute illness. Anti-HAV IgM is invariably present by the time the patient presents and persists for 3 to 6 months after the acute illness.[1] Serum anti-HAV IgG alone indicates past infection (or possibly immunisation) and therefore immunity; it probably persists for life.[1]

4.4.3 Epidemiology

Hepatitis A was a considerable public health problem in Australia in the 1990s. During this time, numerous outbreaks occurred in child day-care centres and preschools,[5] Indigenous communities,[6] communities of men who have sex with men,[7] schools and residential facilities for the disabled,[8] and communities of persons who inject drugs.[7] A very large outbreak of hepatitis A, associated with the consumption of raw oysters, occurred in New South Wales in 1997 and there was a large outbreak associated with semidried tomatoes during 2009.[9,10]

In recent years, hepatitis A notifications and hospitalisations have been low with a downward trend.[11] This has been accompanied by an increasing proportion of cases related to travel to countries where hepatitis A is endemic.[12-14] Advocacy for hepatitis A vaccination of travellers and those at increased risk because of lifestyle or occupation remains a priority, as does the hepatitis A vaccination program for Aboriginal and Torres Strait Islander children. Established initially in north Queensland in 1999 for Indigenous children aged 18 months,[6] the hepatitis A vaccination program was expanded in 2005 to include all Indigenous children aged ≤2 years in the Northern Territory, Queensland, South Australia and Western Australia, contributing substantially to the decline in notifications.[15,16] In north Queensland, most Indigenous children >2 years of age have now been immunised against hepatitis A. However, it is important to note that Indigenous children remain at considerably greater risk – not only of acquiring hepatitis A, but also for being hospitalised with the infection – than non-Indigenous children.[11,17] This is particularly true for Indigenous children residing in other regions of Queensland, the Northern Territory, South Australia and Western Australia. (Refer also to 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

4.4.4 Vaccines

Monovalent hepatitis A vaccines

- ***Avaxim*** – Sanofi-Aventis Australia Pty Ltd (formaldehyde-inactivated hepatitis A virus [GBM strain]). Each 0.5 mL pre-filled syringe contains 160 antigen units of hepatitis A virus (HAV) antigen inactivated by formaldehyde; 0.3 mg aluminium as aluminium hydroxide; 2.5 µL phenoxyethanol; 12.5 µg formaldehyde; ≤5 µg neomycin;<10 ng bovine serum albumin and traces of polysorbate 80.
- ***Havrix Junior*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain]). Each 0.5 mL monodose vial or pre-filled syringe contains 720 ELISA units of HAV antigens; 0.25 mg aluminium as aluminium hydroxide; traces of formaldehyde, neomycin and polysorbate 20.

- ***Havrix 1440*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain]). Each 1.0 mL monodose vial or pre-filled syringe contains 1440 ELISA units of HAV antigens; 0.5 mg aluminium as aluminium hydroxide; traces of formaldehyde, neomycin and polysorbate 20.
- ***Vaqta Paediatric/Adolescent formulation*** – CSL Limited/Merck & Co Inc (formaldehyde-inactivated hepatitis A virus [CR326F strain]). Each 0.5 mL monodose vial or pre-filled syringe contains approximately 25 units (U) of hepatitis A virus protein; 0.225 mg aluminium as aluminium hydroxide; 35 µg borax; traces of formaldehyde, neomycin and bovine serum albumin.
- ***Vaqta Adult formulation*** – CSL Limited/Merck & Co Inc (formaldehyde-inactivated hepatitis A virus [CR326F strain]). Each 1.0 mL monodose vial or pre-filled syringe contains approximately 50 U of hepatitis A virus protein; 0.45 mg aluminium as aluminium hydroxide; 70 µg borax; traces of formaldehyde, neomycin and bovine serum albumin.

Combination vaccines that contain hepatitis A

- ***Twinrix Junior (360/10)*** – GlaxoSmithKline (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 (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.
- ***Vivaxim*** – Sanofi-Aventis Australia Pty Ltd (formaldehyde-inactivated hepatitis A virus [GBM strain] and typhoid Vi capsular polysaccharide). Supplied in a dual-chamber syringe which enables the two vaccines to be mixed just before administration. Each 1.0 mL dose of mixed vaccine contains 160 antigen units of inactivated hepatitis A virus antigen, 25 µg purified typhoid Vi capsular polysaccharide strain Ty2; 0.3 mg aluminium as aluminium hydroxide; 2.5 µL phenoxyethanol; 12.5 µg formaldehyde; ≤5 µg neomycin;<10 ng bovine serum albumin and traces of polysorbate 80.

Inactivated hepatitis A vaccines are prepared from HAV harvested from human diploid cell cultures, which are then purified by ultrafiltration and chromatography, inactivated by formaldehyde, and adsorbed onto aluminium hydroxide adjuvant. Although the vaccines are prepared from differing strains of HAV, there is only one known serotype; immunity induced by a particular strain probably provides protection against all strains.[1]

Inactivated hepatitis A vaccines induce HAV antibodies (anti-HAV) at titres many-fold greater than are provided by the recommended dose of normal human immunoglobulin. Although the vaccines are highly immunogenic (refer below), antibody titres are usually below the detection limits of the routinely available commercial tests for anti-HAV.[1] *Therefore, serological testing to assess immunity after vaccination against hepatitis A is neither necessary nor appropriate*. Likewise, it is also inappropriate to undertake testing if an individual cannot recall if he/she has been vaccinated against hepatitis A in the past; if no vaccination records are available, vaccination should be advised. However, certain groups of people should be screened for natural immunity to hepatitis A to avoid unnecessary vaccination: those born before 1950; those who spent their early childhood in endemic areas; and those with an unexplained previous episode of hepatitis or jaundice. In addition, it is necessary to test for other causes of hepatitis, in particular hepatitis B, in those with unexplained jaundice.

Hepatitis A vaccines are highly immunogenic in both children and adults, with virtually universal seroconversion 4 weeks after vaccination.[1,18,19] Two randomised clinical trials conducted in the early 1990s showed that the vaccines have a very high protective efficacy, approaching 100%.[20,21] This finding is supported by the apparent eradication of hepatitis A from Indigenous communities in north Queensland and the Northern Territory since the introduction of the vaccination program in those regions.[6,16]

The duration of immunity, and therefore protection, following vaccination is not certain. However, vaccine-induced anti-HAV probably persists for many years. There is no current evidence that booster doses are required; in healthy individuals, it is quite possible that they will never be required.[22]

4.4.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[23] Store at +2°C to +8°C. Do not freeze.

4.4.6 Dosage and administration

Inactivated hepatitis A vaccines are to be given by IM injection. The recommended doses and schedules are shown in Table 4.4.1.

Table 4.4.1: Recommended doses and schedules for use of inactivated hepatitis A and hepatitis A combination vaccines*

Vaccine	Age of vaccine recipient (years)	Dose (HAV antigen)	Volume per dose (mL)	Number of doses	Vaccination schedule
Monovalent hepatitis A vaccines					
Avaxim	≥2	160 antigen U	0.5	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 36 months after 1st dose
Havrix Junior	2–<16	720 ELISA U	0.5	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 12 months after 1st dose
Havrix 1440	≥16	1440 ELISA U	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 12 months after 1st dose
Vaqta Paediatric/ Adolescent	1–<18	25 U	0.5	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 18 months after 1st dose
Vaqta Adult	≥18	50 U	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 18 months after 1st dose
Combination hepatitis A/hepatitis B vaccines					
Twinrix Junior (360/10)	1–<16	360 ELISA U	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)†	1–<16	720 ELISA U	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 12 months after 1st dose
Twinrix (720/20)	≥16	720 ELISA U	1.0	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	720 ELISA U	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 *Note*: This accelerated schedule is not suitable for all circumstances.‡
Combination hepatitis A/typhoid vaccine					
Vivaxim	≥16	160 antigen U	1.0	1 (+ 1 monovalent hepatitis A vaccine)	1st dose: single dose of Vivaxim (mixed vaccine) on day 0 (day of vaccination) 2nd dose: for long-term protection against hepatitis A, a 2nd dose of hepatitis A-containing vaccine (monovalent hepatitis A vaccine) should be given between 6 and 36 months after the dose of Vivaxim

* For more information on combination hepatitis A/hepatitis B vaccines and schedules, refer also to 4.5 *Hepatitis B*.

† This schedule should not be used for persons 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.

‡ This 'accelerated' schedule should be used only if there is very limited time before departure to either moderately or highly endemic regions (refer also to 4.5 *Hepatitis B*, 'Accelerated schedules').

Co-administration with other vaccines

Hepatitis A vaccines are inactivated vaccines and can be administered either simultaneously with, or at any time before or after, all other vaccines relevant to international travel.[24]

Combination hepatitis A/hepatitis B vaccines can be administered simultaneously with, or at any time before or after, all other vaccines relevant to international travel.

The combination hepatitis A/typhoid vaccine can be administered simultaneously with, or at any time before or after, all other vaccines relevant to international travel.

Interchangeability of hepatitis A vaccines

Although the manufacturers use slightly different production methods and quantify the HAV antigen content in their respective vaccines differently, the hepatitis A vaccines of the different manufacturers used in 'equivalent' schedules in Table 4.4.1 can be considered interchangeable, when given in a 2-dose course. As there is only one brand of combination hepatitis A/hepatitis B vaccine, interchangeability is not relevant. (Refer also to 'Recommendations for the use of combination hepatitis A/hepatitis B vaccines' in 4.4.7 *Recommendations* below.)

4.4.7 Recommendations

Hepatitis A vaccination is recommended for persons with an increased risk of acquiring hepatitis A and/or who are at increased risk of severe disease. Serological testing for immunity to hepatitis A from previous infection is not usually required prior to vaccination, but may be indicated in some circumstances (refer to 'Serological testing for hepatitis A immunity from infection and/or vaccination' below).

When vaccination against both hepatitis A and hepatitis B (or hepatitis A and typhoid) is indicated, combination vaccines may be used, as described below.

Recommendations for hepatitis A vaccine

Hepatitis A vaccination is recommended for the following groups:

Aboriginal and Torres Strait Islander children residing in the Northern Territory, Queensland, South Australia and Western Australia

Two doses of hepatitis A vaccine are required for Aboriginal and Torres Strait Islander children living in these jurisdictions, due to the increased risk for hepatitis A in this population (refer to 4.4.3 *Epidemiology* above). Vaccination for these children should commence in the 2nd year of life, with the 1st dose given between 12 and 18 months of age, and the 2nd dose given between 18 and 24 months of age. The recommended interval between doses is 6 months (refer to Table 4.4.1). State/territory health authorities should be contacted about local hepatitis A vaccination schedules, including catch-up.

Travellers (≥1 year of age) to hepatitis A endemic areas

Travellers to (≥1 year of age) and expatriates living in moderately to highly endemic areas for hepatitis A should receive hepatitis A vaccine.[25] A single dose of a monovalent hepatitis A vaccine provides protective levels of anti-HAV for at least a year;[1] a 2nd dose is recommended 6 to 12 months following the 1st dose, to increase the duration of protection (refer to Table 4.4.1).

Persons whose occupation puts them at increased risk of acquiring hepatitis A

Persons whose occupation puts them at increased risk of acquiring hepatitis A include: persons who live or work in rural and remote Indigenous communities and/or persons who regularly provide care for Aboriginal and Torres Strait Islander children in the Northern Territory, Queensland, South Australia and Western Australia; staff working in early childhood education and care; carers of persons with developmental disabilities; and plumbers or sewage workers. Refer also to 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*.

Persons whose lifestyle puts them at increased risk of acquiring hepatitis A

Persons who engage in certain sexual practices such as anal intercourse (including men who have sex with men and sex industry workers) and persons who inject drugs (including inmates of correctional facilities) may be at increased risk of acquiring hepatitis A. Refer also to 4.4.3 *Epidemiology* above and 3.3 *Groups with special vaccination requirements*.

Persons with developmental disabilities

Vaccination is recommended for persons with developmental disabilities, and susceptible carers, who attend both residential and non-residential facilities for persons with developmental disabilities. Although conditions/measures to

limit the likelihood of hepatitis A transmission in such facilities have improved in recent decades, outbreaks of hepatitis A can occur in these settings.[26]

Persons with chronic liver disease, liver solid organ transplant recipients and/or those chronically infected with either hepatitis B or hepatitis C viruses

Hepatitis A vaccination is recommended for persons with chronic liver disease of any aetiology.[2,26] Those with chronic liver disease of mild to moderate severity mount a satisfactory immune response following vaccination, but those with end-stage liver disease do not respond as well, and liver transplant recipients may not respond at all.[27,28] Nevertheless, all those with chronic liver disease who are non-immune to hepatitis A should be vaccinated, preferably as early in the course of the disease as possible.

Vaccination is recommended for persons with chronic hepatitis C and hepatitis B infection because of the high case-fatality rate among these persons if they acquire hepatitis A.[2]

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. Vaccination is usually provided in a 3-dose schedule (refer to Table 4.4.1). Twinrix (720/20) can be administered in a 2-dose regimen in persons 1 to <16 years of age (refer to Table 4.4.1); however, this regimen should not be used in 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. 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 A vaccines' above). The use of schedules mixing combination hepatitis A/hepatitis B vaccines with the respective monovalent vaccines is not routinely recommended.

Persons in whom combination hepatitis A/hepatitis B vaccines may be suitable for use include:

- travellers to and expatriates living in moderately to highly endemic areas (for hepatitis A and B)

  The combination hepatitis A/hepatitis B vaccine is recommended in a 3-dose schedule, administered prior to travel. Twinrix (720/20) can be administered according to a 'rapid' schedule if there is limited time before departure.[29] This consists of a single dose on each of days 0, 7 and 21, followed by a 4th dose 12 months after the 1st dose. It is important that a 4th dose be given to ensure longer-term protection (refer to Table 4.4.1).
- 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*).

Refer to 'Recommendations for hepatitis A vaccine' above and 4.5 *Hepatitis B* for more details. Refer also to 3.3 *Groups with special vaccination requirements*.

Recommendations for the use of combination hepatitis A/typhoid vaccine

The combination hepatitis A/typhoid vaccine (refer to Table 4.4.1) is recommended as an option for all persons ≥16 years of age who intend travelling to developing countries where there is an increased risk of acquiring hepatitis A and typhoid fever. This combination is particularly useful for those already immunised against hepatitis B.

To provide longer-term protection against hepatitis A, a single dose of a monovalent adult formulation hepatitis A vaccine administered between 6 and 36 months after the single dose of combination hepatitis A/typhoid vaccine is required (refer to Table 4.4.1). If there is a continued risk of typhoid infection, a booster dose of parenteral typhoid Vi polysaccharide vaccine is required 3 years after the single dose of combination hepatitis A/typhoid vaccine. The combination hepatitis A/typhoid vaccine may be used as a 'booster' vaccine for hepatitis A if a person received a previous dose of a monovalent adult formulation hepatitis A vaccine; this should be given at a minimum interval of 6 months after the 1st dose of hepatitis A vaccine.

Serological testing for hepatitis A immunity from infection and/or vaccination

Serological testing for immunity to hepatitis A is not recommended before routine administration of hepatitis A vaccine to those in most of the categories above, for example, Aboriginal and Torres Strait Islander children or travellers. However, previous infection with hepatitis A is more likely to have occurred in persons born before 1950, those who spent their early childhood in an endemic area, and those with an unexplained previous episode of hepatitis or jaundice.

In such persons, testing for total hepatitis A antibodies or anti-HAV IgG may be indicated, and, if positive, indicates immunity to hepatitis A. Such persons do not need hepatitis A vaccination.

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 vaccination is not routinely required.

4.4.8 Pregnancy and breastfeeding

Hepatitis A vaccine is not routinely recommended for pregnant or breastfeeding women, but can be given where vaccination is considered necessary (refer to 4.4.7 *Recommendations* above).

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

4.4.9 Contraindications

The only absolute contraindications to hepatitis A vaccines are:

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

Combination vaccines containing the hepatitis B component are contraindicated in persons with a history of anaphylaxis to yeast.

4.4.10 Adverse events

The most common adverse events following administration of hepatitis A vaccines are mild local events of a short duration, probably caused by the aluminium hydroxide adjuvant. About 15% of adults report headache and approximately 5% report malaise or fatigue following vaccination.[26] Up to 20% of children who receive either Havrix or Vaqta experience soreness at the injection site. In both adults and children, systemic adverse events such as headache and fever are much less common than local adverse events.[26]

Hepatitis A vaccines do not affect liver enzyme levels. They can be safely given to persons with HIV infection, and do not adversely affect either the HIV load or $CD4^+$ cell count.[30]

4.4.11 Public health management of hepatitis A

Hepatitis A is a notifiable disease in all states and territories in Australia. Detailed information regarding the management of hepatitis A cases and contacts can be found in the national guidelines for control of hepatitis A[31] (www.health.gov.au/cdnasongs).

Further instructions can also 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*).

Post-exposure prophylaxis using hepatitis A vaccine or normal human immunoglobulin (NHIG) can be used to prevent secondary cases in close contacts of hepatitis A cases. However, vaccination is recommended in preference to NHIG for use in post-exposure prophylaxis in persons ≥12 months of age who are immunocompetent (refer to Part 5 *Passive immunisation*).[31]

4.4.12 Variations from product information

None.

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

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